UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

DATE: **10/27/2020**

SUBJECT: **Fluindapyr:** Human Health Risk Assessment for Section 3 Registration and Tolerance Requests for a New Active Ingredient Proposed for Use on Cereal Grains Crop Group 15 except Rice; Forage, Fodder and Straw of Cereal Grains Crop Group 16; Nut, Tree, Group 14-12; Soybean; Ornamentals; and Turf.

PC Code: 138008
Decision No.: 541034

Petition No.: 8F8685
Risk Assessment Type: Single Chemical Aggregate
TXR No.: NA
MRID Nos.: NA

DP Barcode: D447769
File Symbols: 279-GAGI; 279-GAGT; 279-GAUE; 279-GAUG
Regulatory Action: Section 3
Case No.: NA
CAS No.: 1383809-87-7
40 CFR: NA

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1.0 Executive Summary

The Health Effects Division (HED) has conducted a human health risk assessment to evaluate first uses of the active ingredient (ai) fluindapyr, 3-(difluoromethyl)-*N*-(7-fluoro-1,1,3-trimethyl-2,3-dihydro-1*H*-inden-4-yl)-1-methyl-1*H*-pyrazole-4-carboxamide. Fluindapyr is a new ai in the group 7 fungicides and is a pyrazole carboxamide pesticide. The pesticidal mode of action for fluindapyr is as a succinate dehydrogenase inhibitor (SDHI). Fluindapyr is formulated as a soluble concentrate (SC) for proposed postemergent treatment to provide fungal control on cereal grains and soybeans. Fluindapyr is formulated as a racemic mixture of R and S stereoisomers.

Use Profile
The registrant, FMC Corporation, has submitted a petition for tolerances and associated registrations to cereal grain, except rice crop group 15, fodder and straw of cereal grains crop group 16, soybean, tree nut group 14-12, turf (golf courses and lawns and landscape areas around public/commercial areas), and ornamentals (in public/commercial landscapes or properties and greenhouses). The proposed technical product is File symbol 279-GAGI. There are 6 proposed end-use products: EPA File Symbols 279-GAGT, 279-GAUE, 279-GAUN, 279-GAUR, 279-GAGO, and 279-GAUG. Fluindapyr products are formulated as SCs with single maximum application rates ranging from 0.068 lb ai/A to 0.27 lb ai/A. Fluindapyr may be applied by aerial, ground, chemigation or handheld application equipment. The proposed labels require baseline attire (i.e., long-sleeved shirt, long pants, shoes, and socks) plus the personal protective equipment (PPE) of chemical-resistant gloves. When applying to ornamentals with handheld equipment, double-layer chemical-resistant gloves are required. The restricted entry interval (REI) is listed as 5 days for de-tasseling field corn and popcorn grown for seed, 14 days for de-tasseling and hand harvesting sweet corn, and 12 hours for all other activities. Pre-harvest intervals (PHIs) range from 7 to 30 days.

Exposure Profile
Humans may be exposed to fluindapyr in food and drinking water since fluindapyr may be applied directly to growing crops, and applications may result in fluindapyr reaching surface and ground sources of drinking water. Based on the use sites and application methods, there is the potential for short- and intermediate-term occupational handler exposure to fluindapyr during mixing/loading and applying activities, as well as postapplication exposure from activities performed where applications have taken place. Residential handler exposures are not anticipated, but residential postapplication exposures are anticipated from the proposed golf course use. Short-term non-occupational exposure from spray drift is possible.

Hazard Characterization & Dose Response Assessment
Fluindapyr produces adverse liver effects that progress with time in treated dogs, while similar effects are not seen in rats and mice at high dose levels (above 330 mg/kg/day in rats and above the limit dose in mice). In dogs, reduced body weight was observed at 8 mg/kg/day, which was used as a chronic toxicity endpoint for risk assessment. Fluindapyr did not demonstrate neurotoxic potential. In the reproduction study, fluindapyr induces substantial adverse reproductive, offspring, and parental effects. These effects occur at the same dose level (PoD was 30 mg/kg/day (NOAEL), and toxicity endpoints seen at the LOAEL of 142/173 mg/kg/day (males/females) and were used as the toxicity endpoints for incidental oral, dermal and inhalation

exposure assessments. Data on *in utero* and postnatal exposures do not indicate any increase in sensitivity of the young animals. In addition, fluindapyr is "not likely to be carcinogenic to humans" and quantitation of cancer risk is not required, nor conducted. However, fluindapyr causes an increase in thyroid follicular hypertrophy/hyperplasia in the parental animals of both F1 and P generations. This finding raises the concern about the potential impact to the developing brain in response to changing thyroid levels brought on by thyroid effect in the parents. A comparative thyroid assay (CTA) is recommended for fluindapyr to address this concern. At this time, a database uncertainty factor (10X) is placed on fluindapyr to address this concern. Therefore, the total uncertainty factor for risk assessment on fluindapyr is 1000x (10x for interspecies uncertainty, 10x for intraspecies difference, and 10x for lack of a CTA), except for acute dietary route of exposure for which the total uncertainty factor is 100x.

For the general population including infants and children, the adverse effects seen at 125 mg/kg in the acute neurotoxicity study in rats were selected as toxicity endpoints, and the NOAEL of 60 mg/kg/day was selected as the PoD for risk assessment. The chronic dietary exposure endpoint and PoD were selected from a 1-year toxicity study in dogs as the toxicity endpoints were observed following long-term dietary exposure. A PoD and toxicity endpoint for incidental oral exposure were derived from the two-generation reproduction study in rats as effects on the offspring is the correct life stage effect and is the appropriate duration. A dermal toxicity study was tested up to the limit dose (1000 mg/kg/day), and no adverse effects were found. However, the study was considered unacceptable and could not be used for risk assessment purposes. The data from the two-generation reproduction study were employed in establishing the toxicity endpoint and PoD for risk assessment. The inhalation endpoints and POD are selected based on the reproduction study; the rationale for selecting the reproduction study for inhalation exposures is the same as that described for dermal exposures.

Dietary Exposure Assessment
Acute assessment inputs included 100% crop treated (PCT) for all commodities, highest average field trial (HAFT) residue values, empirical and default processing factors, and anticipated livestock residues based on calculated livestock dietary burden and tissue transfer rates from the livestock feeding studies. Estimated Drinking Water Concentrations (EDWCs) were modeled by the Environmental Fate and Effects Division (EFED) and included in this assessment.

The acute risk estimates at the 95th percentile of exposure are 3.5% of the acute population-adjusted dose (aPAD) for the general population, and 8.9% of the aPAD for infants (<1 year old, the most highly exposed population subgroup). There are no risks of concern resulting from acute dietary exposure to fluindapyr.

Chronic assessment inputs included 100% PCT for all commodities, field trial mean residue values, empirical and default processing factors, and anticipated livestock residues based on calculated livestock dietary burden and tissue transfer rates from the livestock feeding studies and metabolite ratios from the metabolism studies. EDWCs modeled by EFED were included in this assessment.

The chronic risk estimates are 14% of the chronic population-adjusted dose (cPAD) for the general population, and 33% of the cPAD for infants (<1 year old) and children (1-2 years old), the most highly exposed population subgroups.

The cancer classification of fluindapyr is "not likely to be carcinogenic to humans" and dietary quantitation of cancer risk is not required, nor conducted.

Residential Exposure and Risk Assessment
Based upon the proposed uses of fluindapyr, a residential handler assessment was not conducted. However, fluindapyr is proposed for use on golf course and so a postapplication exposure and risk assessment was conducted. Estimated risks from dermal exposure were not of concern for either adult's margin of exposure (MOE = 19,000), youth 11 to < 16 years old (MOE = 19,000), or kids 6 to < 11 years old (MOE = 16,000).

Aggregate Risk Assessment
In accordance with FQPA, HED must consider and aggregate pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. There is potential for short-term aggregate exposure to fluindapyr via the dietary and residential pathways. Children 6-12 represent the highest dermal exposure from postapplication exposures and the highest background dietary exposure. Therefore, this population subgroup is considered protective of the other population subgroups. Aggregate risks to children (6 to < 11 years) old does not exceed the LOC. The Aggregate Risk Index (ARI) is 5. HED is concerned if the ARI is less than 1.

Occupational Exposure and Risk Assessment
There were no dermal or inhalation risk estimates of concern identified, nor were there any risks of concern from any of the combined MOE estimates when label specified, baseline clothing plus the proposed personal protective equipment (PPE) were assumed. For all uses except turf grass, proposed labels specify baseline clothing and PPE of chemical resistant gloves. For applicators to turf grass and ornamentals using handheld spray equipment, proposed labels specify baseline clothing and PPE of chemical resistant gloves and double-layer clothing. All combined MOEs estimates (dermal + inhalation) for occupational handlers ranged from 1,300 to 1,100,000 with a LOC of 1000.

All but two occupational postapplication dermal assessment risk estimates were not of concern on the day of application (Day 0). Hand harvesting and detasseling activities for sweet corn resulted in an MOE of 460 on the day of application. However, the proposed label specifies a 14-day restricted entry interval. The estimated MOE at day 14 for hand harvesting and hand de-tasseling is 2,000.

Environmental Justice
Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations.[1]"

[1] https://www.epa.gov/laws-regulations/summary-executive-order-12898-federal-actions-address-environmental-justice

Human Studies
This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide to determine their exposure. Appendix C provides additional information on the review of human research used to complete the risk assessment. There is no regulatory barrier to continued reliance on these studies, and all applicable requirements of EPA's Rule for the Protection of Human Subjects of Research (40 CFR Part 26) have been satisfied.

2.0 HED Conclusions

HED recommended that a comparative thyroid assay (CTA) be required to address the uncertainties associated with life stage susceptibility. In the absence of the CTA study, a 10x factor was applied to appropriate exposure scenarios. The additional 10x is not being applied to either the acute or chronic dietary scenarios but is applied to residential post-application scenarios (golf course uses) as well as to occupational exposures.

There are no dietary risks of concern for any duration or population subgroup resulting from the proposed use pattern.

There are no residential postapplication risks of concern from the proposed uses. There are no occupational handler risks of concern, assuming label specified baseline clothing and PPE. There are no occupational post application risks of concern when the label specified 14-day REI for detasseling and hand harvesting is assumed.

As noted in Section 2.2.3, HED has recommended revisions to the petitioned-for tolerances. The petitioner should provide revised Sections B and F to the petition.

The specific tolerance recommendations are discussed in Table 2.2.2.

2.1 Data Deficiencies

None

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

Proposed tolerance enforcement methods for plant commodities include liquid chromatography with tandem mass spectrometers (LC/MS/MS) methods: P3770G (dry bean, grape, soybean seed, sugar beet roots and tops, and wheat straw) for quantitation of residues of fluindapyr and metabolites 3-OH-F9990, F9990-DM-glucoside, 1-OH-Me-F9990, 1-OH-Me-DM-F9990, and 1-COOH-F9990; and RA.17.01 (grape, rapeseed whole plant, straw, and oil, wheat grain, straw, and dry gluten) for quantitation of residues of 1-OH-Me-F9990, 1-OH-Me-DM-F9990, and 1-COOH-F9990. These methods were used as the data collection methods in the plant field studies.

The proposed tolerance enforcement method for livestock commodities is LC/MS/MS method 133SRUS16R0208 (all livestock commodities) which is suitable for quantitation of residues of fluindapyr, DM-F9990, 1-OH-Me-F9990, 1-OH-Me-DM-F9990, and 1-COOH-F9990. This method was also used for data collection in the livestock feeding studies.

HED reviewed the proposed analytical enforcement methods against the TMV (tolerance method validation) checklist contained in the ACB (Analytical Chemistry Branch/BEAD) SOP No. 019, Revision 1.0. Adequate recovery data and chromatograms have been provided at the method limit of quantitation (LOQ). Concurrent fortification recoveries were acceptable in all matrices over the range of expected residues. The methods use standard analytical techniques and commercially available instrumentation. The methods displayed good linearity, specificity, and repeatability, and include the use of two ion transitions (primary quantitation and confirmatory) monitored by MS/MS. Successful Independent Laboratory Validations (ILVs) were completed for methods P3770G and 133SRUS16R0208, but the ILV for method RA17.01 was not successful. Radiovalidation data for plant and livestock commodities generally demonstrated acceptable extraction efficiencies.

Proposed enforcement methods P3770G for crops and 133SRUS16R0208 for livestock are adequate to quantify the residues of concern for tolerance enforcement in their respective matrices (fluindapyr in primary crops, fluindapyr in livestock commodities other than meat byproducts, and fluindapyr plus 1-OH-Me-F9990 in meat byproducts). LOQ per analyte is generally 0.01 ppm, except for residues in milk which have an LOQ of 0.005 ppm. Proposed enforcement method RA17.01 is inadequate to quantify the residues of concern for crops rotated into fields previously treated with fluindapyr. However, as no rotated crop tolerances have been currently petitioned, this does not prevent the requested use pattern from being registered.

The Agency concludes that method P3770G is acceptable for the enforcement of the recommended tolerances of fluindapyr in/on primary crop commodities.

The Agency concludes that method 133SRUS16R0208 is acceptable for the enforcement of the recommended tolerances of fluindapyr in/on livestock commodities.

Recovery of the parent compound from plants is demonstrated to be acceptable through a QuEChERS extraction and analysis, method RA.14.04 using solid-phase extraction (SPE) and quantitation by LC/MS/MS.

2.2.2 Recommended Tolerances

HED has reviewed the available residue data and has determined the appropriate tolerance levels for residues of fluindapyr, which are presented below in Table 2.2.2.

Table 2.2.2. Tolerance Summary for Fluindapyr.			
Commodity/**Correct Commodity Definition**	**Established/ Proposed Tolerance (ppm)**	**HED-Recommended Tolerance (ppm)**	**Comments**
40 CFR §180.xxx (a)(1) "*General.* Tolerances are established for residues of the fungicide fluindapyr, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only fluindapyr, 3-(difluoromethyl)-*N*-(7-fluoro-1,1,3-trimethyl-2,3-dihydro-1*H*-inden-4-yl)-1-methyl-1*H*-pyrazole-4-carboxamide, in or on the commodity			
Almond, hulls	15	15	
Corn, field, grain	--	0.01	*Definition correction, processed commodity tolerance unnecessary*
Field corn, grain	0.01	--	
Field corn, oil	0.03	--	
Corn, sweet, kernel plus cob with husks removed	--	0.01	*Definition corrections*
Sweet corn, K+CHWR	0.01	--	
Corn, sweet, stover	--	20	
Sweet corn, stover	20	--	
Grain, aspirated fractions	--	20	
Aspirated grain fractions	60	--	
Grain, cereal, forage, fodder, and straw, group 16, forage, except rice	--	15	
Grain, cereal, forage, Crop Group 16, except rice, forage	15	--	
Grain, cereal, forage, fodder, and straw, group 16, hay, except rice	--	8	
Grain, cereal, hay, Crop Group 16, except rice, forage	8	--	
Grain, cereal, forage, fodder, and straw, group 16, stover, except rice	--	4	
Grain, cereal, stover, Crop Group 16, except rice, stover	4	--	
Grain, cereal, forage, fodder, and straw, group 16, straw, except rice	--	20	
Grain, cereal, straw, Crop Group 16, except rice, straw	20	--	
Grain, cereal, group 15, except rice and corn	--	0.8	*Difference in calculation*
Grain, cereal, Crop Group 15, except rice and corn	0.9	--	
Nut, tree, group 14-12	--	0.04	*Definition correction*
Tree nuts, crop group 14-12	0.04	--	
Soybean, forage	15	15	
Soybean, hay	30	30	
Soybean, hulls	0.6	0.6	
Soybean, seed	0.2	0.15	*Difference in calculation*
Egg	--	0.01	*Commodities and residue values included are based upon MRBD*
Milk	--	0.01	
Cattle, fat	0.15	0.03	
Cattle, meat	--	0.01	
Goat, fat	--	0.03	
Goat, meat	--	0.01	
Hog, fat	--	0.01	

Table 2.2.2. Tolerance Summary for Fluindapyr.			
Commodity/**Correct Commodity Definition**	**Established/ Proposed Tolerance (ppm)**	**HED-Recommended Tolerance (ppm)**	**Comments**
Hog, meat	--	0.01	
Horse, fat	--	0.03	
Horse, meat	--	0.01	
Poultry, fat	--	0.01	
Poultry, meat	--	0.01	
Sheep, fat	--	0.03	
Sheep, meat	--	0.01	
§180.xxx (a)(2) "Tolerances are established for residues of the fungicide fluindapyr, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring the sum of fluindapyr, 3-(difluoromethyl)-*N*-(7-fluoro-1,1,3-trimethyl-2,3-dihydro-1*H*-inden-4-yl)-1-methyl-1*H*-pyrazole-4-carboxamide, and 3-(difluoromethyl)-*N*-(7-fluoro-1-hydroxymethyl-1,3-dimethyl-2,3-dihydro-l*H*-inden-4-yl)-1-methyl-l*H*-pyrazole-4-carboxamide, calculated as the stoichiometric equivalent of fluindapyr, in or on the commodity." (Meat byproducts)			
Cattle, meat byproducts	0.6	0.3	*Commodities and residue values included are based upon MRBD*
Goat, meat byproducts	--	0.3	
Horse, meat byproducts	--	0.3	
Hog, meat byproducts	--	0.01	
Swine, meat byproducts	0.02	--	
Poultry, meat byproducts	0.03	0.01	
Sheep, meat byproducts	--	0.3	

2.2.3 Revisions to Petitioned-For Tolerances

Petitioned-for tolerances were revised for appropriate commodity and crop group definitions, differences in calculated values (cereal grain, soybean seed, cattle fat, cattle meat, hog meat byproducts, and poultry meat byproducts), and for the inclusion of additional livestock commodities (egg, milk, cattle meat, poultry meat, swine fat, and meat, fat, and meat byproducts of sheep, goat, and horse). A separate tolerance for corn oil is not required.

2.2.4 International Harmonization

There are no Codex or Canada MRLs for fluindapyr.

2.3 Label Recommendations

2.3.1 Recommendations from Residue Reviews

The data do not support the proposed plant-back intervals (PBIs) and restrictions for non-labeled crops. A revised section B of the petition is required, incorporating a 12-month PBI for all crops not on the flunidapyr label, and removing the plant-back restriction for "all other crops."

2.3.2 Recommendations from Residential Exposure Assessment

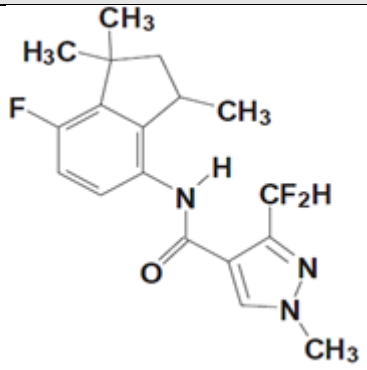
None.

2.3.3 Recommendations from Occupational Exposure Assessment

The minimum spray solution per acre for ground applications needs to be specified for all proposed end-use products. The proposed end-use product EPA Reg. No. 279-GAGT has errors due to the voluntarily canceled use of grapes. Specifically, the second paragraph in subsection "Spray Equipment/Volume" should have "grapes and" deleted and the entire row that includes "7.1 and 0.22" should be eliminated from the "Rate Equivalency Table". Finally, the maximum annual rate for most uses is incorrectly calculated on most proposed labels. Label parameters or use patterns may need to be revised to reflect these findings. (Incorrectly calculated maximum annual rates do not affect the occupational risk assessment.)

3.0 Introduction

3.1 Chemical Identity

Table 3.1. Fluindapyr Nomenclature.	
Chemical Structure	
Common name	Fluindapyr
Company experimental name	F9990
IUPAC name	3-(difluoromethyl)-*N*-[(3*RS*)-7-fluoro-2,3-dihydro-1,1,3-trimethyl-1*H*-inden-4-yl]-1-methyl-1*H*-pyrazole-4-carboxamide
CAS name	3-(difluoromethyl)-*N*-(7-fluoro-2,3-dihydro-1,1,3-trimethyl-1*H*-inden-4-yl)-1-methyl-1*H*-pyrazole-4-carboxamide
CAS #	1383809-87-7

3.2 Physical/Chemical Characteristics

Table 3.2. Physicochemical Properties of Technical Grade Fluindapyr		
Parameter	Value	Reference
Molecular weight (g/mol)	350.36	MRID 50518249
Melting point/range (°C)	160.9 to 170.5	
pH	5.5 (1% w/v aq. soln.)	
Density (g/cm^3)	1.2719	
Water solubility (mg/L at pH 7.3 and 20°C)	1.74	

Table 3.2. Physicochemical Properties of Technical Grade Fluindapyr		
Parameter	Value	Reference
Solvent solubility (mg/L at 20°C)	Toluene > 2 Dichloromethane > 162 Methanol > 80 Acetone > 300 Ethyl acetate > 115 *n*-heptane - 0.316	MRID 50518057
Vapor pressure at 25°C (Pa)	2.85 x 10^{-8}	MRID 50518249
Henry's Law Constant (Pa m^3 mol^{-1})	6.14 x 10 -6	
Dissociation constant (pK_a)	Does not ionize	MRID 50518050
Octanol/water partition coefficient Log(K_{OW}) (pH 7.7 and 20°C)	4.12	MRID 50518249

Fluindapyr is a solid at room temperature and is generally stable, it is not anticipated to change phase under typical storage conditions. Due to its low vapor pressure, loss to volatilization is not expected. The compound has relatively low solubility in aqueous matrices and high solubility in organic matrices. The log(K_{OW}) indicates that the parent compound may partition into fatty matrices.

3.3 Pesticide Use Pattern

Fluindapyr is proposed for postemergence foliar applications to cereal grains except rice (crop group 15), soybeans, nut trees (crop groups 14-12), ornamentals (in greenhouses; in non-agricultural commercial or institutional landscape settings; and in container-grown or in field-grown settings), and turf (in golf courses and commercial/institutional landscaping). The proposed technical product is EPA File Symbol 279-GAGI. There are 6 proposed end-use products: EPA Reg. Nos. 279-GAGT, 279-GAUE, 279-GAUN, 279-GAGO, 279-GUAR and 279-GAUG. Fluindapyr may be applied by aerial, ground, chemigation or handheld application equipment. Fluindapyr products are formulated as SCs with single maximum application rates ranging from 0.078 lb ai/A (corn, soybean, wheat, and grain sorghum) to 0.270 lb ai/A (turf and ornamentals). All proposed labels require baseline attire (i.e., long-sleeved shirt, pants, shoes, and socks) plus the personal protective equipment (PPE) of chemical-resistant gloves. Two labels, 279-GAGO and 279-GAUR require the aforementioned and requires double layer torso protection for applicators using handheld sprayers applying to landscape ornamentals.

A summary of the representative proposed agricultural and commercial use sites with the highest application rates or percent active ingredient (ai) is provided in Table 3.3.1. A detailed summary of all end use products is found in the occupational and residential exposure and risk assessment conducted for this action (L. Bacon, E. Lang, D455860, 10/27/2020).

Table 3.3.1. Summary of Proposed Directions for Use of Fluindapyr based on Maximum Rates.							
Formulation [EPA Reg. No.]	**Proposed Sites**	**Application Timing, Type, and Equipment**	**Application Rate (lb ai/A)**	**Max. No. Applic. per Season**	**Max. Annual Application Rate (lb ai/A/yr)**	**PHI (days)**	**Use Directions and Limitations**
F9944-74 (279-GAGT) (4.0 lb ai/gal SC)	Almond/ Walnut/ Pecans/ Other Tree Nuts	Broadcast foliar applications by ground, airblast, or aerial	0.109 to 0.150 lb ai/A	3	0.450 lb ai/A/yr	30	Do not apply by handheld sprayer. 10 GPA for aerial applications; GPA for ground applications not specified; REI is 12 hours. 7-14-day RTI.
	Cereal Grains except Rice (Crop Group 15)[1]	Broadcast foliar applications by ground, airblast, or aerial	0.078 to 0.134 lb ai/A	2	0.268 lb ai/A/yr	7-30	Do not apply by manually pressurized handgun on sweet corn. 3 GPA for aerial applications; GPA for ground applications not specified; REI for hand harvesting and detasseling sweet corn is 14 days; REI for all other activities is 12 hours; 10-14 day RTI
	Soybean	Broadcast foliar applications by ground, airblast, or aerial	0.078 to 0.110 lb ai/A	2	0.230 lb ai/A/yr	7-21	3 GPA for aerial applications; GPA for ground applications not specified; REI is 12 hours. 14 day RTI
F9944-74 T&O SC Fungicide (279-GAGO) (4.0 lb ai/gal SC)	Turf Grass – Golf Courses & Commercial Landscaping	Broadcast foliar application via chemigation	0.18 to 0.27 lb ai/A or 0.0042 to 0.0063 lb ai/gal	4	1.1 lb ai/A/yr	NA	Do not apply to athletic fields. 43-87 GPA for chemigation; REI is not specified – only "do not enter until spray has dried"; 7-28 day RTI.
	Ornamentals	Broadcast foliar application via chemigation or mechanically pressurized handwand	0.0018 to 0.0027 lb ai/gal	4	1.1 lb ai/A/yr	NA	Do not allow people (other than applicators) or pets on treatment area during application. Do not enter treatment area until spray has dried. For applications to landscaping ornamentals with mechanically-pressurized handguns, applicators must wear a double layer and gloves. 100 GPA for handheld sprayers; GPA for chemigation not specified; REI is not specified – "do not enter until spray has dried"; 7-14 day RTI.

lb ai/A = pounds of active ingredient per acre; lb ai/gal = pounds of active ingredient per gallon of water; PHI = pre-harvest interval; GPA = gallons per acre; REI = restricted entry interval; RTI = re-treatment interval; NA = not applicable

[1] Cereal Grains except rice (Crop Group 15) include: corn (grain, feed, seed, pop, and sweet), grain sorghum, wheat – summer & winter, triticale, and barley.

3.4 Anticipated Exposure Pathways

As fluindapyr may be applied directly to growing crops, potential dietary exposures exist from consuming treated commodities, as well as exposure to secondary residues in livestock commodities resulting from livestock consuming treated feedstuffs, and from residues which run off of treated fields and are transported to drinking water sources. Residential handler exposure is not anticipated, but residential postapplication exposures are anticipated based on the proposed use to golf courses. Short-term non-occupational exposure from spray drift is possible. There is the potential for short- and intermediate-term occupational handler exposure to fluindapyr during mixing/loading and applying activities, as well as postapplication exposure from activities performed where applications have taken place. This risk assessment considers the relevant exposure pathways based on all of the proposed uses of fluindapyr.

3.5 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (https://www.archives.gov/files/federal-register/executive-orders/pdf/12898.pdf). As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the U.S. Department of Agriculture's National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age and ethnic group. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas postapplication are evaluated. Spray drift can also potentially result in postapplication exposure and it is also being considered whenever appropriate. Further considerations are also currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to other types of possible bystander exposures and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 Hazard Characterization and Dose-Response Assessment

Fluindapyr is a new pesticide and is proposed to be used as a broad-spectrum fungicide. It belongs to the SDHI class of fungicides. The mode of fungicidal action for this class of compound is by binding to the ubiquinone binding site of the SDH enzyme leading to blockage of the tricarboxylic acid (TCA) cycle at the level of succinate and fumarate oxidation. The eventual effect is inhibition of cellular respiration in fungi. However, mode of action data in mammals is not available for fluindapyr.

4.1 Toxicology Studies Available for Analysis

The required toxicity studies on fluindapyr are available except an immunotoxicity study and an unacceptable 28-day dermal toxicity study. The 28-day dermal toxicity study was classified as unacceptable due to faulty dermal application method. However, the requirements for these two studies were recommended to be waived (Camp, J., TXR 0057980, 12/04/2019). The two-generation reproduction study showed an increase in the incidence of thyroid follicular hypertrophy/hyperplasia in the parental animals (P and F1), and this finding triggered the consideration for the need of a CTA. (Camp, J., TXR 0057980, 12/04/2019).

The studies available for this evaluation are:

- Subchronic oral toxicity studies in rats, dogs and mice;
- Combined chronic toxicity/carcinogenicity study in rats;
- Chronic toxicity study in dogs;
- Carcinogenicity study in mice;
- Developmental toxicity studies in rats and rabbits;
- Reproduction study in rats;
- Acute and subchronic neurotoxicity studies in rats;
- Mutagenicity battery of studies;
- Metabolism studies in rats and *in vitro* metabolism study with hepatocytes;
- 28-day inhalation study in rats;

The toxicity profile table (Appendix A) contains brief summaries of all studies submitted.

Recommendation to Require Comparative Thyroid Assay for Fluindapyr: The two-generation reproduction study showed an increase in the incidence of thyroid follicular hypertrophy/hyperplasia in the parental animals (P and F1), and this finding triggered the consideration for the need of a CTA. A CTA is recommended to be required for fluindapyr. In the absence of these data, HED has applied a 10x uncertainty factor, for data base uncertainty, to all exposure scenarios except for the acute dietary and chronic dietary. The 10X UF_{DB} will not be applied to the acute and chronic dietary PODs, because perturbation of thyroid after a single dose is not anticipated to impact the developing fetus or offspring, and because the chronic dietary endpoint, based on effects in dogs, is protective of potential thyroid-related effects observed in developing rats or offspring. (Camp, J., TXR 0058009, 3/25/2020).

4.2 Absorption, Distribution, Metabolism, & Elimination (ADME)

With oral administration (dietary or gavage), fluindapyr was absorbed rapidly. Much of the absorption occurred within 24 hours after dosing, with approximately 75% and 73% of the administered dose (AD) absorbed by males and females, respectively. By 48 hours post dosing, greater than 90% AD was absorbed by both males and females. The results indicated a T_{max} for plasma concentration was 2.0 and 3.0 hours (hrs.) for males and females, respectively. An estimated $t_{1/2}$ for plasma concentration was approximately 5.6 and 5.2 hrs. for males and females, respectively.

After absorption, the radioactivity was distributed to all major organs. Two hours post dosing, highest concentrations were found in the liver (≈5% AD), kidneys (≈0.6 %AD), gastrointestinal tract (GI) (≈6%AD), and skin (≈3%AD). The major portion (≈ 90%) of the absorbed dose was eliminated by 48-hr post dosing. After 168 hours postdosing, none of the tissues contained more than 0.1% AD.

The absorbed fluindapyr was metabolized rapidly and extensively, and at least 50 metabolites were identified. Metabolism was mainly through *N*-demethylation, oxidation of methyl groups to hydroxymethyl and further to carboxylic acid. Additional metabolites, to a lesser extent, were also formed through double hydroxylation, dehydrogenation and conjugation with glucuronic acid. With bile duct cannulation study, the major metabolites (>10% AD in bile and urine) included 1-hydroxymethyl-fluindapyr, 1-hyroxymethyl-*N*-desmethyl-fluindapr, 1-carboxy-fluindapyr, 1-carboxy-*N*-desmethyl-fluindapyr and *N*-hydroxy-fluindapyr.

Excretion occurred predominantly via feces (≈ 72% AD) and a smaller amount via urine (≈26% AD). Negligible amounts of radioactivity were recovered in expired air (<0.01%) or recovered from the carcass (< 0.5%). The elimination profiles of the compound in both male and female rats were similar, and essentially no bioaccumulation occurred. The unchanged parent compound elimination was similar in both genders, ranging between 5 and 15% of AD.

4.2.1 Dermal Absorption

The only dermal absorption study available is an *in vitro* dermal penetration study with excised human skin. The results showed the potentially absorbed doses (receptor fluid, receptor chamber wash, skin, and stratum corneum [tape strips 3-20]) for SC concentrate and two aqueous dilutions (4200, 260, and 3.0 µg/cm^2), were 0.14%, 0.71%, and 2.99% of the applied dose, respectively. At the present time, the Agency does not rely solely on *in vitro* data to derive a dermal absorption factor (DAF). However, the human *in vitro* study could be used if animal *in vivo* and *in vitro* studies were submitted to complete a triple pack.

At this time, a DAF of 17% was recommended based on the DAF's of structurally related chemicals with similar mode of fungicidal action (penflufen, sedaxane, fluxapyroxad benzovindiflupyr, fluindapyr, and penthiopyrad). The DAFs for structurally related chemicals ranged from 5.4% to 17% based on *in vivo* dermal penetration studies or extrapolation of oral/dermal studies.

4.3 Toxicological Effects

The oral subchronic (90-day and 28-day) toxicity studies in rats and mice showed no adverse effects up to the highest dose tested (330 mg/kg/day for rats and 1339 mg/k/day for mice). In contrast, in the 90-day dog study (capsule), adverse liver effects included hepatocellular hypertrophy, increased liver weights, and bile duct hyperplasia with correlated increases in alkaline phosphatase (ALP), alanine aminotransferase (ALT), and gamma glutamyl transferase (GGT) at the highest dose tested (200 mg/kg/day). The adverse liver effects were progressive in dogs with respect to the duration of exposure as indicated by the data of the one-year dog study (capsule). For the one-year toxicity study, fluindapyr produced similar adverse liver effects at a

dose (40 mg/kg/day), approximately 5 times lower than that of the subchronic study (200 mg/kg/day). Most of the clinical pathology changes were statistically significant and above the reference values for common chemistry determinations in adult dogs[2].

There were no adverse liver effects seen in the rat combined chronic/ carcinogenicity study up to the limit dose (1000 mg/kg/day); however, adverse liver effects were seen in the mouse carcinogenicity study at a higher dose level (412 mg/kg/day) than the liver effects observed in dogs; the effects consisted of increased incidence of hepatocellular alterations (basophilic, eosinophilic, vacuolated), necrosis, and pigmented macrophages.

With *in-utero* exposure in the developmental toxicity studies, fluindapyr did not produce any adverse effects in either rat or rabbit parental animals or fetuses at or approaching the limit dose (1000 mg/kg/day). In the reproduction study, in parental animals (P and F1 males and females), fluindapyr induced an increase in thyroid follicular hypertrophy/hyperplasia. It also induced adverse effects on a host of reproductive parameters, which included corpora lutea vacuolation, increased epithelium mucification, increased anestrous epithelium of the vagina, delayed vaginal opening, and decrease in antral follicle counts, increase in seminal vesicle weight, decreases in ovary and uterine weights, and attenuated endometrium. It also produced adverse offspring effects as indicated by decreases in F1 and F2 pup body weights in both sexes; thymus and spleen weights were also decreased. The parental, reproductive, and offspring effects all occurred at the same dose levels. The increased incidence of thyroid follicular hypertrophy/hyperplasia raised concerns for the potential of thyroid effects on the developing animals. The Hazard and Science Policy Council (HASPOC) analyzed the toxicity and exposure data of fluindapyr and recommended that a CTA be required to address the uncertainties associated with life stage susceptibility and allow for the establishment of points of departure (PoDs) that would be protective of potential effects of thyroid function disruption in pregnant females on the fetus and newborn (Camp, J., TXR 0057980, 12/04/2019).

Fluindapyr did not demonstrate neurotoxic potential in the subchronic neurotoxicity study. However, in the acute neurotoxicity study, potential evidence of neurotoxicity in the form of decreases in total and ambulatory motor activities and in rearing were seen at approximately 5 hours after dosing (time for peak plasma concentration of fluindapyr). No additional functional observation (FOB) parameters were affected, and no neuropathological findings of both central and peripheral nerves were observed.

The technical grade fluindapyr has low acute oral toxicity (Toxicity Category III), and low dermal and inhalation acute toxicity (Toxicity Category III, IV respectively). It is not an eye or dermal irritant and a dermal sensitizer.

All six of the proposed end-use products have low acute toxicity, with the highest route of exposure being Category III (acute oral) and requiring a Signal word CAUTION. These products are negative for skin sensitization.

[2] Klaassen, JK. (1999). Reference Values in Veterinary Medicine. Laboratory Medicine. 1999; 30 (3): 194-197

Fluindapyr exhibited low acute toxicity with oral, dermal, and inhalation dosing resulting in Toxicity Category III for oral and dermal routes of exposure and IV for inhalation route of exposure. It was not an eye or dermal irritant, but it produced moderate skin sensitization with local lymph node assay.

4.4 Safety Factor for Infants and Children (FQPA Safety Factor)[3]

As described in Section 4.3, due to the adverse finding of thyroid follicular hypertrophy/hyperplasia in parental males and females (P and F1), a CTA is recommended, and it follows that a 10x FQPA safety factor is needed for all exposure assessments (except acute dietary exposure) to address the uncertainties associated with life stage susceptibility.

4.4.1 Completeness of the Toxicology Database

As discussed in the previous two sections, a CTA is recommended; however, the currently available data are adequate for conducting human health risk assessment with appropriate uncertainty factors.

4.4.2 Evidence of Neurotoxicity

In the acute neurotoxicity study (ACN), decreases in total and ambulatory motor activities and in rearing were seen and could be considered as potential evidence for neurotoxicity. However, concern is low because 1) no other effects were observed in database including in the subchronic neurotoxicity study (SCN), 2) no neurohistopathology was found in the ACN, SCN or any toxicity study in the fluindapyr database, and 3) the toxicity endpoints and PoD selected for risk assessment are protective of the effects seen in the ACN.

4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

There is no evidence of increased quantitative or qualitative susceptibility in the developmental toxicity studies in rabbits or rats or the reproductive toxicity study in rats.

4.4.4 Residual Uncertainty in the Exposure Database

There are no residual uncertainties in the exposure database. The dietary risk assessments are based on high-end assumptions such as 100% CT assumptions, HAFT and field trial mean residue values, empirical and default processing factors, anticipated livestock residues based on calculated livestock dietary burden and tissue transfer rates from the livestock feeding studies and modeled, high-end estimates of residues in drinking water. All of the exposure estimates are based on high-end assumptions and are not likely to underestimate risk.

[3] HED's standard toxicological, exposure, and risk assessment approaches are consistent with the requirements of EPA's children's environmental health policy (https://www.epa.gov/children/epas-policy-evaluating-risk-children).

4.5 Toxicity Endpoint and Point of Departure Selections

A summary of selected toxicity endpoints and PoDs for risk assessment are presented in Table 4.5.3.1, and the details for each exposure scenario are presented below.

Acute Dietary Exposure Endpoint
For the general population including infants and children, the adverse effects seen at 125 mg/kg in the acute neurotoxicity study in rats were selected as toxicity endpoints, and the NOAEL of 60 mg/kg/day was selected as the PoD for risk assessment. The adverse effects included decreases in total and ambulatory motor activities in males and females, as well as decreased rearing in females at 5 hours postdosing. Uncertainty factors for interspecies extrapolation (10x) and intraspecies variation (10x) were applied to the NOAEL to calculate the acute reference dose (aRfD = 0.6 mg/kg). The aPAD (0.6 mg/kg) is equal to the aRfD divided by the FQPA SF of 1x. The additional FQPA SF/UF_{db} is not applicable for acute dietary exposure because perturbation of thyroid after a single dose is not anticipated to result in developmental effects in the young animals.

Chronic Dietary Exposure Endpoint
The chronic dietary exposure endpoint and PoD were selected from a 1-year toxicity study in dogs as the toxicity endpoints were observed following long-term dietary exposure. The LOAEL of 8 mg/kg/day was based on decreased body weights (↓10-15%). The NOAEL/PoD was 4 mg/kg/day. This PoD is protective of all effects following chronic exposure, including the adverse effects observed in the chronic/carcinogenicity study in rats (increased incidence of uterine endometrial hyperplasia) as well as the parental, offspring, and reproductive effects noted in the 2-generation reproduction study. Uncertainty factors for interspecies extrapolation (10x) and intraspecies variation (10x) were applied to the NOAEL of the 1-year study in dogs to calculate the chronic reference dose (cRfD = 0.04 mg /kg/day).

In considering the FQPA safety factor (FQPA SF) for the chronic dietary exposure assessment, ordinarily a 10x safety factor would be applied to this POD to account for lack of CTA. The additional 10x SF would be applied to address the potential impacts on the developing brain in response to adverse thyroid levels on the parental animals. In the case of fluindapyr, a safety factor of 1x is judged to be sufficiently protective in the context of risk assessment considerations. The reasons are:

- The thyroid follicular cell hypertrophy/hyperplasia, based on which a CTA study is required, in parental animals occurred at 143 mg/kg/day (LOAEL); in contrast, the adverse effect (decrease in body weights) which defined the toxicity endpoint from the chronic dog study happened at 8 mg/kg/day (LOAEL). This set of data indicates approximately 17x higher dose level where the thyroid effect was seen.

- Using the toxicity endpoint in the dog study to assess the chronic dietary exposure risk is protective of the thyroid effect seen in the rat. This is particularly apparent when considering the Human equivalent dose (HED) derived by conducting a Body $Weight^{3/4}$ scaling analysis for different species of test animals (dog and rat) (please see table below). Under the current conditions, the toxicity endpoint from the dog

provides adequate protection for the potential impact of thyroid effects on the fetus and newborn.

Table 4.5 Derived Human equivalent dose (HED)		
Study	**LOAEL (mg/kg/day)**	**HED (mg/kg/day)**
Chronic Toxicity Dogs	8	5.1
Reproduction rats	142	34

- Finally, in context of PoD analysis. if the chronic toxicity endpoint was to be based on the thyroid effect and the resulting PoD would be 30 mg/kg/day. With the use of this toxicity endpoint, an FQPA SF of 10x would be needed; this would yield a population adjusted RfD of 0.03 mg/kg/day. This is quite similar to that using the toxicity endpoint from the chronic toxicity study in dogs with an FQPA SF of 1x (RfD=0.04 mg/kg/day).

Incidental Oral Exposure Endpoints (all durations)
A PoD and toxicity endpoint for incidental oral exposure were derived from the two-generation reproduction study in rats as effects on the offspring is the correct life stage effect and is the appropriate duration. The PoD was 30 mg/kg/day (NOAEL), and toxicity endpoints seen at the LOAEL of 142/173 mg/kg/day (males/females) were based on: offspring effects (decrease F1 & F2 pup body weights, and decreases in thymus and spleen weights), parental effects (increased incidence of thyroid hyperplasia/ hypertrophy), and reproductive effects (corpora lutea vacuolation, increase epithelium mucification, increase anestrous epithelium of the vagina, delayed vaginal opening, increase in acyclic cycles with corresponding decrease in regular cycles, decrease in antral follicle counts, increase in seminal vesicle weight, decreases in ovary and uterine weights, and attenuated endometrium). The LOC for incidental oral exposures is 1000x (10x for intra species variation and 10x for interspecies differences and 10x FQPA SF/UF_{DB}).

Dermal Exposure Endpoints
A dermal toxicity study (MRID 50518097) was tested up to the limit dose (1000 mg/kg/day), and no adverse effects were found. However, the study was considered unacceptable and could not be used for risk assessment purposes. The reason is there was a major flaw in the dermal application procedure; the test substance was a powder, which should be dissolved or suspend in suitable vehicle then applied to the testing area, whereas in this study the powder was placed directly on a gauze, which was attached to the test area. Hence, the data from the two-generation reproduction study were used in establishing the toxicity endpoint and POD for risk assessment. The PoD was 30 mg/kg/day (NOAEL), and toxicity endpoints seen at the LOAEL of 142/173 mg/kg/day (males/females) were based on offspring effects (decreased F1 & F2 pup body weights, and decreases in thymus and spleen weights), parental (increased incidence of thyroid hyperplasia/ hypertrophy) and reproductive effects (corpora lutea vacuolation, increase epithelium mucification, increase anestrous epithelium of the vagina, delayed vaginal opening, increase in acyclic cycles with corresponding decrease in regular cycles, decrease in antral follicle counts, increase in seminal vesicle weight, decreases in ovary and uterine weights, and

attenuated endometrium). Since the previous ToxSAC memo was finalized, an additional 10X FQPA safety factor (SF)/UF_{DB} has been applied to the dermal POD for the lack of the CTA study. The updated LOC for dermal exposures is 1000 (10x for intra species variation and 10x for interspecies differences and 10x FQPA SF/UF_{DB}). A dermal absorption factor of 17% should be employed for dermal risk assessment(see Section 4.2.1).

Inhalation Exposure Endpoints (all durations
Prior to HASPOC evaluation, an inhalation endpoint and POD were not selected for risk assessment. Although hunched posture, decrease activity, and abnormal gait were observed at the highest concentration, 0.98 mg/L (which was essentially the limit concentration, 1 mg/L), ToxSAC concluded that the effects seen in the 4-week inhalation study (MRID 50518101) were not adverse since they did not persist at 5 hours post exposure. Therefore, a LOAEC was not established. The NOAEC was the highest concentration tested (0.98 mg/L).

However, based on indications of thyroid toxicity (thyroid hyperplasia/hypertrophy) in parental animals in the multigeneration reproductive toxicity study in rats (MRID 50518108), ToxSAC and HASPOC identified the residual uncertainty related to the potential impact of fluindapyr on thyroid function during critical developmental stages. Consequently, the HASPOC recommended requiring the CTA which, in turn, necessitated the conduct of an inhalation assessment since potential life-stage sensitivity is not addressed in the guideline inhalation study. The inhalation endpoints and POD are selected based on the reproduction study; the rationale for selecting the reproduction study for inhalation exposures is the same as that described for dermal exposures. In addition, the safety factors for the inhalation exposure assessment (along with the associated rationale for such safety factors) is identical to that described for the dermal exposure assessment section above.

In conclusion, Table 4.5.3.1 and 4.5.3.2 summarize the toxicity endpoints and PoD's for risk assessment for fluindapyr.

4.5.1 Recommendation for Combining Routes of Exposures for Risk Assessment

The toxicity endpoints selected for incidental oral, inhalation, and dermal routes of exposure are the same; therefore, these routes of exposure could be combined to assess aggregate risks.

4.5.2 Cancer Classification and Risk Assessment Recommendation

Fluindapyr produced a slight increase in hepatocellular adenomas in male CD-1 mice. The tumor incidence and related toxicology data were evaluated by the Cancer Assessment Review Committee (CARC), which classified fluindapyr as "Not Likely to be Carcinogenic to Humans". This was based on the lack of treatment-related tumors seen in male or female rats or mice and no concern for mutagenicity (CARC Report. Louden, R. TXR 0057930, 09/03/2019). Quantification of carcinogenic potential is not required for fluindapyr.

4.5.3 Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

Table 4.5.3.1 Summary of Toxicological Doses and Endpoints for Fluindapyr for Use in Dietary and Non-Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty/FQPA Safety Factors**	**RfD, PAD, LOC for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary (General Population, including Infants and Children)	NOAEL= 60 mg/kg	UF_A= 10x UF_H= 10x FQPA SF= 1x	Acute RfD = aPAD =0.6 mg/kg/day	Acute neurotoxicity study LOAEL = 125 mg/kg based on decreased total and ambulatory motor activities in both sexes, and decreased rearing in females on Day 0.
Chronic Dietary (All Populations)	NOAEL= 4 mg/kg/day	UF_A= 10x UF_H= 10x FQPA SF/UF_{db} = 1x	Chronic RfD = cPAD = 0.04 mg/kg/day	1-year oral toxicity in dogs (capsule) LOAEL = 8 mg/kg/day based decreased body weight (↓10-15%).
Incidental Oral Short-Term (1-30 days)	NOAEL= 30 mg/kg/day	UF_A= 10x UF_H= 10x FQPA SF/UF_{db} = 10x	LOC = 1000	Two-generation reproduction study LOAEL =142 mg/kg/day based on offspring, parental, and reproductive effects[+]
Dermal Short (1-30days)- and Intermediate-Term (1-6 months)	NOAEL= 30 mg/kg/day DAF = 17%	UF_A= 10x UF_H= 10x FQPA SF/UF_{db} = 10x	LOC = 1000	Two-generation reproduction study LOAEL =142 mg/kg/day based on offspring, parental, and reproductive effects[+]
Inhalation Short- (1-30 days) and Intermediate-Term (1-6 months)	NOAEL= 30 mg/kg/day	UF_A= 10x UF_H= 10x FQPA SF/UF_{db} = 10x	LOC = 1000	Two-generation reproduction study LOAEL =142 mg/kg/day based on offspring, parental, and reproductive effects[+]
Cancer (oral, dermal, inhalation)	Fluindapyr is classified as "not likely to be carcinogenic to humans" and quantitation of cancer risk is not required			

Point of Departure (PoD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). SF = Safety Factor. UF_{db} = data base uncertainty factor due to the requirement for a comparative thyroid assay (CTA). PAD = population-adjusted dose (a = acute, c = chronic). RfD = reference dose. LOC = level of concern.

[+]: Off spring effects: decrease F1 & F2 pup body weights and decreases in thymus and spleen weights.

Parental effects: increased incidence of thyroid hyperplasia/ hypertrophy.

Reproductive effects: corpora lutea vacuolation, increase epithelium mucification, increase anestrous epithelium of the vagina, delayed vaginal opening, increase in acyclic cycles (with corresponding decrease in regular cycles), decrease in antral follicle counts, increase in seminal vesicle weight, decreases in ovary and uterine weights, and attenuated endometrium.

Table 4.5.3.2. Summary of Toxicological Doses and Endpoints for Fluindapyr for Use in Occupational Human Health Risk Assessments				
Exposure/ Scenarios	Point of Departure	Uncertainty/ Safety Factor	RFD, PAD, LOC	Study and Toxicological Effects
Dermal Short (1-30-days) and Intermediate-Term (1-6 months)	NOAEL= 30 mg/kg/day DAF = 17%	UF_A= 10x UF_H= 10x FQPA SF/UF_{db} = 10x	LOC = 1000	Two-generation reproduction study LOAEL =142 mg/kg/day based on offspring, parental, and reproductive effects+
Inhalation Short- (1-30 days) and Intermediate-Term (1-6 months)	NOAEL= 30 mg/kg/day	UF_A= 10x UF_H= 10x FQPA SF/UF_{db} = 10x	LOC = 1000	Two-generation reproduction study LOAEL =142 mg/kg/day based on offspring, parental, and reproductive effects+
Cancer (oral, dermal, inhalation)	Fluindapyr is classified as "not likely to be carcinogenic to humans" and quantitation of cancer risk is not required			

Point of Departure (PoD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). SF = Safety Factor. UF_{db} = data base uncertainty factor due to the requirement for a comparative thyroid assay (CTA). PAD = population-adjusted dose (a = acute, c = chronic). RfD = reference dose. LOC = level of concern.

+: Off spring effects: decrease F1 & F2 pup body weights, thymus and in spleen weights.
Parental effects: increased incidence of thyroid hyperplasia/ hypertrophy.
Reproductive effects: corpora lutea vacuolation, increase epithelium mucification, increase anestrous epithelium of the vagina, delayed vaginal opening, increase in acyclic cycles (with corresponding decrease in regular cycles), decrease in antral follicle counts, increase in seminal vesicle weight, decreases in ovary and uterine weights, and attenuated endometrium.

5.0 Dietary Exposure and Risk Assessment

5.1 Residues of Concern Summary and Rationale

The HED Residues of Concern Knowledgebase Subcommittee (ROCKS) met on 11/13/2019 to discuss the residues of concern for fluindapyr in plants, livestock, rotational crops, and drinking water (Negussie, M. D454238, 11/13/2019). Their recommendations are listed below in Table 5.1.

Table 5.1. Summary of Metabolites and Degradates to be Included in the Risk Assessment and Tolerance Expression.[1]			
Matrix		Residues Included in Risk Assessment	Residues Included in Tolerance Expression
Plants	Primary Crop	Fluindapyr, 3-OH-F9990, 1-OH-Me-F9990, 1-OH-Me-F9990-*O*-glucoside, DM-F9990-*N*-glucoside, 1-OH-Me-DM-F9990, 1-COOH-F9990	Fluindapyr

Table 5.1. Summary of Metabolites and Degradates to be Included in the Risk Assessment and Tolerance Expression.[1]			
Matrix		Residues Included in Risk Assessment	Residues Included in Tolerance Expression
	Rotational Crop	Fluindapyr, 1-COOH-F9990, 1-OH-Me-F9990	Fluindapyr, 1-COOH-F9990, 1-OH-Me-F9990
Livestock	Ruminant	Fluindapyr, 1-COOH-F9990, 1-OH-Me-F9990, 1-OH-Me-DM-F9990	Fluindapyr, (All commodities except meat byproducts)
	Poultry	Fluindapyr, DM-F9990, 1-OH-Me-F9990, 1-OH-Me-DM-F9990	Meat byproducts- Fluindapyr and 1-OH-Me-F9990
Drinking Water		Fluindapyr, 3-OH-F9990 and 1-COOH-F9990	Not Applicable

[1] Fluindapyr = fluindapyr, 3-(difluoromethyl)-*N*-(7-fluoro-1,1,3-trimethyl-2,3-dihydro-1*H*-inden-4-yl)-1-methyl-1*H*-pyrazole-4-carboxamide
3-OH-F9990 = 3-(difluoromethyl)-*N*-(7-fluoro-3-hydroxy-1,1,3-trimethyl-2,3-dihydro-l*H*-inden-4-yl)-1-methyl-l*H*-pyrazole-4-carboxamide
1-OH-Me-F9990 = 3-(difluoromethyl)-*N*-(7-fluoro-1-hydroxymethyl-1,3-dimethyl-2,3-dihydro-l*H*-indene-4-yl)-1-methyl-l*H*-pyrazole-4-carboxamide
1-OH-Me-F9990-*O*-glucoside = 1-OH-Me-F9990-*O*-glucoside = 3-(difluoromethyl)-*N*-(7-fluoro-1-(β-*D*-glucosyl)-oxymethyl-1,3-dimethyl-2,3-dihydro-l*H*-inden-4-yl)-1-methyl-l*H*-pyrazole-4-carboxamide
DM-F9990-*N*-glucoside =
1-OH-ME-DM-F9990 = 3-(difluoromethyl)-*N*-[7-fluoro-1-(hydroxymethyl)-1,3-dimethyl-2,3-dihydro-1*H*-indene-4-yl]-1*H*-pyrazole-4-carboxamide
1-COOH-F9990 = (difluoromethyl)-1-methyl-1*H*-pyrazole-4-carboxamido)-7-fluoro-1,3-dimethyl-2,3-dihydro-1*H*-indene-1-carboxylic acid

5.1.1 Primary Crop Metabolism Summary

The parent fluindapyr was the predominant residue component (except soybean and sugar beet) in plant metabolism studies. In addition, 3-OH-F9990, 1-OH-Me-F9990, 1-OH-Me-F9990-O-glucoside, and in soybean DM-F9990-N-glucoside, pyr-amide, and DM-F9990-n-serine were major in the primary crop metabolism studies. Fluindapyr, 3-OH-F9990, and 1-OH-Me-F9990, F9990-DM-glucoside, and 1-OH-Me-DM-F9990 were analyzed in the field trials. These studies indicated that the highest expected residues would be from parent fluindapyr, except for wheat grain; therefore, the parent is suitable residue to monitor for misuse in primary crops. The ROCKS recommends parent fluindapyr for tolerance enforcement and parent fluindapyr, 3-OH-F9990, 1-OH-Me-F9990, 1-OH-Me-F9990-O-glucoside, DM-F9990-N-glucoside, 1-OH-ME-DM-F9990, and 1-COOH-F9990 residues of concern for risk assessment.

5.1.2 Rotational Crop Degradation Summary

Fluindapyr was found in all rotational crop matrices at all PBIs. The major residues in rotational crops were 3-OH-F9990, 1-OH-Me-F9990, 1-COOH-F9990, N-DesMe-Pyr acid, pyrazole carboxylic acid, and pyrazole carboxamide. The toxicity concern for the pyrazole derived metabolites (metabolites with only the pyrazole ring) is expected to be significantly less than the parent molecule, as they are naturally occurring in animals in minute quantities, are excreted much more rapidly than the parent compound, and lack two of the three ring structures of the parent as well as the indane amine bridge; therefore, these compounds were not included as residues of concern. Field rotational crop studies analyzed for fluindapyr, 3-OH-F9990, 1-OH-Me-F9990, and 1-COOH-F9990. The results indicate that metabolite 1-COOH-F9990 was

quantifiable (>LOQ) on mustard greens and radish tops and 1-OH-Me-F9990 on wheat straw. The ROCKS recommends parent fluindapyr, 3-OH-F9990, 1-OH-Me-F9990, and 1-COOH-F9990 should be considered residues of concern for rotational crops for tolerance and risk assessment.

5.1.3 Livestock Metabolism Summary

For ruminants and poultry, based on the results of the metabolism studies and feeding studies, fluindapyr was the major residue in fat. Significant amounts of 1-COOH-F9990, 1-OH-Me-F9990, 1-OH-Me-DM-F9990, DM-F9990, and 1-SO_4-Me-F9990 were also detected. For livestock (except meat byproducts), the ROCKS recommends parent fluindapyr as the residue of concern for tolerance enforcement. The major residues in poultry (fluindapyr, DM-F9990, 1-OH-Me-F9990, 1-OH-Me-DM-F9990) and ruminants (fluindapyr, 1-COOH-F9990, 1-OH-Me-F9990, 1-OH-Me-DM-F9990) should be considered residues of concern for risk assessment. In livestock metabolism studies and feeding studies, metabolite 1-OH-Me-F9990 was a major residue. For meat byproducts of poultry and ruminants, the ROCKS recommends parent fluindapyr and 1-OH-Me-F9990 as the residue of concern for tolerance enforcement.

5.1.4 Drinking Water Degradation and Fate Summary

The parent fluindapyr is persistent. The persistence of its five identified degradation products is uncertain based on the durations of available studies. The degradates are calculated to be more mobile than the parent. Three of these degradates were present at >10% applied radioactivity (i.e., major) and are similar in structure to the parent. Parent could run-off to surface waters or (limited) leach to groundwater and may also be carried by drift to adjacent terrestrial and aquatic systems. Parent fluindapyr degrades slowly in the environment for most dissipation pathways. Based on the aerobic and anerobic soil and aquatic metabolism studies and the terrestrial field studies, the ROCKS recommends that the residues of concern in drinking water are parent fluindapyr and its three major metabolites 3-OH-F9990, and cis- and trans- 1-COOH-F9990. These degradates may be more mobile and soluble than the parent, and thus may be more available for both surface water runoff to drinking water reservoirs and leaching to groundwater. The mean K_{OC} value of 1764 L/kg-oc indicates that fluindapyr is slightly mobile and movement through the soil profile will be slow; however, it is persistent and may still move into groundwater (P. Engel, D447798, xx/xx/2020). Residues of concern in drinking water are not applicable for tolerance enforcement.

5.2 Food Residue Profile

Acceptable residue chemistry data are available including metabolism studies, storage stability studies, field trial studies, processing studies, and livestock feeding studies. The database is adequate to assess the proposed uses of fluindapyr for purposes of tolerance enforcement and risk assessment.

Generally, fluindapyr residues are quantifiable in crop commodities resulting from the proposed use pattern. The compound is not found to concentrate readily in processed high-water matrices, concentrates slightly upon dehydration, concentrates readily in high-oil matrices, and is

otherwise stable to processing (such as high temperature hydrolysis). Livestock feedstuffs are found to have much higher residues than foodstuffs from the same plant, and quantifiable secondary residues in livestock commodities are expected especially in liver and kidney, but also in any fatty matrices. Detectible residues are expected in rotated crops.

5.3 Water Residue Profile

The EDWCs used in the dietary risk assessment were provided by EFED in the following memorandum: "Fluindapyr: Drinking Water Assessment (DWA) for the Proposed New Chemical Registration" (D447798, Engel, P. 06/18/2020) and incorporated directly into this dietary assessment. Water residues were incorporated in the DEEM-FCID into the food categories "water, direct, all sources" and "water, indirect, all sources."

Fluindapyr and relevant transformation products (3-OH-F9990 and 1-COOH-F9990) were modeled as ROC using the total residue approach. EDWCs were modeled using the Pesticide Water Calculator (PWC, version 1.52) for surface water and groundwater. For acute and chronic scenarios, groundwater residues were greater than surface water residues, and as such the highest groundwater concentrations have been incorporated into these assessments.

Based on maximum label use rates (on turf and ornamentals), EDWCs are not expected to exceed 254 µg/L (groundwater peak concentration), and 218 µg/L average (groundwater postbreakthrough). Recommended EDWCs are provided in Table 5.3.

Table 5.3. Estimated Drinking Water Concentrations of Fluindapyr

Use and Model	Acute EDWC (µg/L)	Chronic EDWC (µg/L)
Surface Water [PWC 1.52]	42.1	29.4 (non-cancer)
		20.7 (cancer)
Groundwater [PWC 1.52]	**254**	**218**

The bolded values are used in these assessments.

The drinking water models and their descriptions are available at the EPA internet site: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/about-water-exposure-models-used-pesticide.

5.4 Dietary Risk Assessment

5.4.1 Description of Residue Data Used in Dietary Assessment

Residue input values are based on field trial data including the parent and monitored metabolites. While not all residues of concern for risk assessment were monitored in crop field trials and the ruminant feeding study, the residue values observed in these data were corrected for the contribution of total residues of concern observed in the metabolism studies. All residue values, including drinking water estimates, in both the acute and chronic assessments were incorporated as point estimates.

Empirical processing factors derived from acceptable processing studies and 2018 Dietary Exposure Scientific Advisory Council (DESAC) default processing factors were used in this assessment. A summary of the acute and chronic dietary exposure and risk estimates is provided in Table 5.4.6 below.

5.4.2 Percent Crop Treated Used in Dietary Assessment

For both acute and chronic assessments, 100% crop treated was assumed for all commodities.

5.4.3 Acute Dietary Risk Assessment

The results of the acute dietary exposure and risk assessment at the 95th percentile of exposure are reported in Table 5.4.6., below. The dietary exposure of fluindapyr to the general population is 3.5% of the aPAD. The dietary exposure of fluindapyr to all infants (<1 year old), the most highly exposed subgroup, is 8.9% of the aPAD.

5.4.4 Chronic Dietary Risk Assessment

The results of the chronic dietary (food plus water) exposure and risk assessment are reported in the summary Table 5.4.6., below. Chronic dietary exposures to fluindapyr result in risks estimates of 14% of the cPAD for the general U.S. population and 33% of the cPAD for infants <1 year old, the most highly exposed population subgroup.

A critical commodity contribution analysis was conducted for infants (<1 year old) and children (1-2 years old) to determine commodities contributing >5% of total exposure for these subgroups. For infants (<1 year old), the primary risk driver is drinking water (88% of exposure). For children (1-2 years old), the primary risk driver is drinking water (65% of exposure), and secondary risk drivers are milk (8.6%), grape juice (5.5%), and wheat flour (5.5%).

5.4.5 Cancer Dietary Risk Assessment

The cancer classification of fluindapyr is “not likely to be carcinogenic to humans;” therefore, cancer risk is not of concern.

5.4.6 Summary Table

Table 5.4.6. Summary of Dietary (Food and Drinking Water) Exposure and Risk for Fluindapyr.

Population Subgroup	Acute Dietary (95th Percentile)		Chronic Dietary	
	Dietary Exposure (mg/kg/day)	% aPAD*	Dietary Exposure (mg/kg/day)	% cPAD*
General U.S. Population	0.020863	3.5	0.005537	14
All Infants (<1 year old)	**0.053274**	**8.9**	**0.013349**	**33**
Children 1-2 years old	0.049576	8.3	0.010193	26
Children 3-5 years old	0.037424	6.2	0.008184	21

Table 5.4.6. Summary of Dietary (Food and Drinking Water) Exposure and Risk for Fluindapyr.				
Population Subgroup	Acute Dietary (95th Percentile)		Chronic Dietary	
	Dietary Exposure (mg/kg/day)	% aPAD*	Dietary Exposure (mg/kg/day)	% cPAD*
Children 6-12 years old	0.022711	3.8	0.005552	14
Youth 13-19 years old	0.015740	2.6	0.004133	10
Adults 20-49 years old	0.018122	3.0	0.005288	13
Adults 50-99 years old	0.016527	2.8	0.005179	13
Females 13-49 years old	0.018386	3.1	0.005230	13

*The subpopulation(s) with the highest risk estimates are bolded.

6.0 Residential Exposure/Risk Characterization

Based on the proposed uses of fluindapyr, residential handler exposure is not expected. However, fluindapyr is proposed for use on golf course turf, and so residential postapplication exposure was assessed.

6.1 Residential Postapplication Exposure/Risk Characterization

There is the potential for postapplication exposure for individuals exposed as a result of being in an environment that has been previously treated with fluindapyr. The quantitative exposure/risk assessment for residential postapplication exposures is based on potential dermal exposure as a result of applications of fluindapyr to turf (golf courses) for adults, youth 11 to <16 years old, and youth 6 to <11 years old.

Turf Transferable Residue (TTR): Chemical specific TTR data were not submitted for fluindapyr.

In accordance with 40 CFR part 158, TTR data are required for all occupational or residential turf uses (e.g., sod farms, golf courses, parks, and recreational areas) that could result in postapplication exposure to turf. In the absence of chemical specific TTR data, EPA uses default values. The *2012 Standard Operating Procedures for Residential Pesticide Exposure Assessment* includes an analysis of all TTR data, available at the time, which resulted in the selection of revised liquid and granular default values for the fraction of the application rate available for transfer after a turf application (F_{AR}). These values are based on an analysis of 59 TTR studies performed with the Modified California Roller Method (36 studies using liquids, 11 studies using wettable powders/water dispersible granules, and 12 studies using granules). The liquid results (N=131) indicate a range of F_{AR} values from 0.0005% to 6.1% and the granular results (N=37) indicate a range of 0.00064% to 0.69%. In both the liquid and granular data, a large range of transferability is observed and this variability can potentially be attributable to many factors such as active ingredient; formulation; field conditions in the studies; weather conditions (e.g., humidity); or many other difficult to quantify factors. Although witnessed across multiple chemicals, this range in F_{AR} values is not expected when considering TTR data for a single chemical. HED selected 1% and 0.2% as high-end default values for liquid and granular products, respectively. Because TTR data are not available for fluindapyr, EPA is using

the default value of 1% for liquid products. Although there may be a small degree of uncertainty in the use of the default TTR value for fluindapyr (i.e., there is a small chance that the F_{AR} value may exceed the applicable default value), it is likely that the health-protective aspects of EPA's residential and occupational postapplication turf assessment methodology will more than compensate for this potential uncertainty (i.e., the methodology is likely to overestimate exposure by a factor greater than the factor than the highest measured F_{AR} values exceed the defaults). For example, when assessing residential postapplication turf exposure, EPA assumes the following: exposures occur to zero-day (i.e., day of application) residues every day of the assessed exposure duration (i.e., EPA assumes that no dissipation or degradation occurs, it doesn't rain, the grass is not mowed, etc); individuals perform the same postapplication activities performed in the turf transfer coefficient study day after day (e.g., tumbling, playing on turf with toys, etc.); and individuals engage in these postapplication activities for a high-end amount of time every day that is represented by data reflecting time children spend outdoors and not specifically engaged in activities on turf, when in actuality children do not spend all of their outdoor time on turf and high-end levels of activity will not occur every day.

Given the conservatisms discussed above and the potential compounding nature of these conservatisms, EPA is able to rely upon the calculated exposure estimates with confidence that exposure is not being underestimated.

HED estimates indicate that the residential turf postapplication exposure for golf courses using default TTR values for fluindapyr is minimal in comparison to the level of concern. That is, the calculated MOE for adults (MOE = 19,000), youth (MOE = 19,000) and children (MOE = 16,000) is greater than 10 times higher than the level of concern (LOC = 1000). In this instance, it is unlikely that chemical specific TTR data would be needed to further refine exposure assessments or would add appreciably to our general understanding of the availability of turf transferable pesticide residues. Consequently, EPA is waiving the 40 CFR TTR data requirement at this time.

Summary of Residential Postapplication Non-Cancer Exposure and Risk Estimates

Postapplication residential dermal exposures are anticipated from the proposed use of fluindapyr on golf course turf. The LOC for all routes of exposure is 1,000. Adult, youth (11 to <16 years old), and children (6 to <11 years old) dermal short-term residential postapplication exposures to treated turf (golf courses) resulted in no risk estimates of concern, where dermal MOEs ranged from16,000 to 19,000. The summary of risk estimates are found in Table 6.1.1.

Table 6.1.1. Residential Postapplication Non-cancer Exposure and Risk Estimates for Fluindapyr.

Lifestage	Postapplication Exposure Scenario		Application Rate[1] (lb ai/A)	Dose (mg/kg/day)[2]	MOEs[3] LOC=1,000
	Use Site	Route of Exposure			
Adult	Golfing	Dermal	0.27	0.001568	19,000
Youth 11 to <16 years old				0.001575	19,000
Child 6 to <11 years old				0.001849	16,000

1 Based on proposed label (EPA Reg. No. 279-GAGO).

2 Dose (mg/kg/day) algorithms provided in 2012 Residential SOPs (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide).

3 $\text{MOE} = \frac{POD\ (mg\ kg^{-1}day^{-1})}{Dose\ (mg\ kg^{-1}day^{-1})}$.

6.2 Residential Risk Estimates for Use in Aggregate Assessment

The proposed use of fluindapyr on golf course turf results in residential postapplication exposure, appropriate for aggregation with background dietary exposures. Table 6.2.1 reflects the residential risk estimates that are recommended for use in the aggregate assessment for fluindapyr.

- The recommended residential exposure for the adults aggregate assessment is dermal exposures from postapplication exposure to residue from treated golf course.
- The recommended residential exposure for youth (11 to <16 yrs old) aggregate assessment is dermal exposures from postapplication exposure to residue from treated golf course.
- The recommended residential exposure for child (6 to <11 yrs old) aggregate assessment is dermal exposures from postapplication exposure to residue from treated golf course.

Table 6.2.1. Recommendations for the Residential Exposures for the Fluindapyr Aggregate Assessment.

Lifestage	Exposure Scenario	Dose (mg/kg/day)[1]				MOE[2]			
		Dermal	Inhalation	Oral	Total	Dermal	Inhalation	Oral	Total
Adult	Turf - Golf	0.0016	NA	NA	0.0016	19,000	NA	NA	19,000
Youth 11 to <16 yrs		0.0016			0.0016				
Youth 6 to <11 yrs		0.0018			0.0018	16,000			16,000

1 Dose = the highest dose for each applicable life stage of all residential scenarios assessed. Total = dermal + inhalation + incidental oral (where applicable).

2 $\text{MOE} = \frac{POD\ (mg\ kg^{-1}day^{-1})}{Dose\ (mg\ kg^{-1}day^{-1})}$.

7.0 Aggregate Exposure/Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure.

The proposed uses of fluindapyr to golf course results in residential dermal postapplication exposures of short-term duration appropriate for aggregation. Of the population subgroups for which postapplication exposure to golf courses is assessed, children 6-12 represent the highest dermal exposure from postapplication exposures and the highest background dietary exposure. Therefore, this population subgroup is considered protective of the other population subgroups (i.e., protective of youth 11 < 16 years old, and adults). Because the LOC for chronic dietary

exposures (considered background exposure) differs from that of dermal exposures, it is appropriate to extimate aggregate exposure and risk using an aggregate risk indext (ARI) approach. Aggregate risks to children (6 to < 11 years) old does not exceed the LOC. The ARI is 5. HED is concerned if the ARI is less than 1. Fluindapyr is classified as "not likely to be carcinogenic to humans;" therefore, cancer risk is not a concern.

7.1 Acute Aggregate Risk

The acute aggregate risk assessment is equivalent to the acute dietary risk assessment discussed in Section 5.4.3. All risk estimates are not of concern.

7.2 Short-Term Aggregate Risk

There is potential short-term aggregate exposure to fluindapyr via dietary (which is considered background exposure) and residential (which is considered primary) exposure pathways. For a description of the residential exposure scenarios considered in the aggregate assessment, see Section 6.2. Table 7.2.1 summarizes the aggregate risk estimate.

Table 7.2.1 Short-Term Aggregate Risk Calculations for Fluindapyr

Population	Short-Term Scenario								
	Dietary Exposure (LOC = 100)[1,4]		Oral Residential Exposure		Dermal Residential Exposure[2,5] (LOC = 1000)		Inhalation Residential Exposure		Aggregate ARI[3,6]
	MOE	ARI	MOE	ARI	MOE	ARI	MOE	ARI	
Children 6 – 12 years old	720	7.2	NA	NA	16225	16.2	NA	NA	5

HED is concerned if the ARI is less than 1. ARI = Aggregate Risk Index. MOE = Margin of Exposure.
1: MOE Dietary = [(chronic POD, mg/kg/day)/(chronic dietary exposure)]. ARI dietary = [(MOE dietary)/(MOE LOC)].
2: MOE Dermal = [(dermal POD, mg/kg/day)/dermal exposure. ARI dermal = [(MOE dermal)/MOE LOC)]
3: ARI Aggregate = 1/[(1/ARI dietary+ (1/ARI incidental oral) + (1/ARI inhalation)], where applicable.
4: MOE Dietary for kids 6 – 12 years old: MOE dietary = [4 mg/kg/day/0.005552 mg/kg/day = 720]. ARI dietary = [720/100 = 7.2]
5: MOE Dermal for kids 6 < 11 years old: MOE dermal = [30 mg.kg/day / 0.001849 mg/kg/day = 16225] ARI dermal = [16225/1000 = 16.2].
6: Aggregate ARI: 1/1/7.2 + 1/16.2 = 5

7.3 Intermediate-Term Aggregate Risk

Intermediate-term aggregate assessments include exposures that will occur from thirty days to six months. For adults, intermediate-term exposure is not expected for the residential exposure pathway. Therefore, the intermediate-term aggregate risk is equivalent to the chronic dietary exposure estimates described in Section 5.4.4. All risk estimates are not of concern.

7.4 Chronic Aggregate Risk

The chronic aggregate risk assessment results from long-term exposure to residues in food and drinking water since there are no residential scenarios that result in long-term exposure. The chronic dietary exposure analysis includes both food and drinking water and, therefore, the

chronic aggregate risk assessment is equivalent to the chronic dietary risk assessment discussed in Section 5.4.4. All risk estimates are not of concern.

8.0 Non-Occupational Spray Drift Exposure and Risk Estimates

Spray drift is a potential source of exposure to those nearby pesticide applications. This is particularly the case with aerial application, but, to a lesser extent, spray drift can also be a potential source of exposure from the ground application methods (e.g., groundboom) employed for fluindapyr. The Agency has been working with the Spray Drift Task Force (a task force composed of various registrants which was developed as a result of a Data Call-In issued by EPA), EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices (see the Agency's Spray Drift website for more information).[4] The agency has also developed a policy on how to appropriately consider spray drift as a potential source of exposure in risk assessments for pesticides. The potential for spray drift will be quantitatively evaluated for each pesticide during the *Registration Review* process which ensures that all uses for that pesticide will be considered concurrently. The approach is outlined in the revised (2012) *Standard Operating Procedures for Residential Risk Assessment (SOPs) - Residential Exposure Assessment Standard Operating Procedures Addenda 1: Consideration of Spray Drift.* This document outlines the quantification of indirect non-occupational exposure to drift.

9.0 Non-Occupational Bystander PostApplication Inhalation Exposure and Risk Estimates

Volatilization of pesticides may be a source of postapplication inhalation exposure to individuals nearby pesticide applications. The agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-0687-0037). The agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219).
During Registration Review, the agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for fluindapyr.

10.0 Cumulative Exposure/Risk Characterization

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to fluindapyr and any other substances and fluindapyr does not appear to produce a toxic metabolite produced by other substances. For the purposes of this action, therefore, EPA has not assumed that fluindapyr has a common mechanism of toxicity with other substances. In 2016, EPA's Office of Pesticide Programs released a guidance document entitled, *Pesticide Cumulative Risk Assessment: Framework for Screening Analysis* [https://www.epa.gov/pesticide-science-

[4] Available: http://www.epa.gov/reducing-pesticide-drift

and-assessing-pesticide-risks/pesticide-cumulative-risk-assessment-framework]. This document provides guidance on how to screen groups of pesticides for cumulative evaluation using a two-step approach beginning with the evaluation of available toxicological information and if necessary, followed by a risk-based screening approach. This framework supplements the existing guidance documents for establishing common mechanism groups (CMGs)[5] and conducting cumulative risk assessments (CRA)[6]. During Registration Review, the agency will utilize this framework to determine if the available toxicological data for fluindapyr suggests a candidate CMG may be established with other pesticides. If a CMG is established, a screening-level toxicology and exposure analysis may be conducted to provide an initial screen for multiple pesticide exposure.

11.0 Occupational Exposure/Risk Characterization

11.1 Short-/Intermediate-Term Occupational Handler Exposure and Risk Estimates

Based on the proposed use patterns and labeling, types of equipment and techniques that can potentially be used, short- and intermediate-term occupational handler exposure is expected from the proposed uses of the new ai fungicide, fluindapyr. The quantitative exposure and risk assessment developed for occupational handlers is based on the scenarios listed in Table 11.1.1. The proposed fluindapyr product labels direct mixers (M), loaders (L), applicators (A), and other handlers to wear a baseline layer of clothing (i.e., a single layer of clothing consisting of a long-sleeved shirt and long pants, shoes plus socks) plus the PPE of waterproof or chemical-resistant gloves for all uses except M/L/A users of handheld sprayers to ornamental sites for which the proposed PPE is a double layer [torso] plus waterproof or chemical-resistant gloves.

Summary of Occupational Handler Non-Cancer Exposure and Risk Estimates

Estimates of dermal and inhalation exposure were calculated for various levels of PPE. Results are presented for baseline clothing with protective gloves or double layer torso with protective gloves as determined by the proposed clothing and PPE language on the labels. The adult body weight of 69 kg was used for the assessment since the dermal and inhalation PODs are based on developmental and/or fetal effects.

All of the occupational handler combined dermal and inhalation risk estimates were above the LOC of 1,000 considering at baseline plus the proposed PPE of chemical-resistant gloves or in the case of applicators with hand equipment at ornamental sites, double layer plus chemical-resistant gloves. All combined (dermal + inhalation) MOEs ranged from 1,300 to 1,100,000. See Table 11.1.1. for additional details.

The Agency matches quantitative occupational exposure assessment with appropriate characterization of exposure potential. While HED presents quantitative risk estimates for human flaggers where appropriate, agricultural aviation has changed dramatically over the past two decades. According the 2012 National Agricultural Aviation Association (NAAA) survey of

[5] *Guidance for Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity* (USEPA, 1999)

[6] *Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity* (USEPA, 2002)

their membership, the use of GPS for swath guidance in agricultural aviation has grown steadily from the mid 1990's. Over the same time period, the use of human flaggers for aerial pesticide applications has decreased steadily from ~15% in the late 1990's to only 1% in the most recent (2012) NAAA survey. The Agency will continue to monitor all available information sources to best assess and characterize the exposure potential for human flaggers in agricultural aerial applications.

HED has no data to assess exposures to pilots using open cockpits. The only data available is for exposure to pilots in enclosed cockpits. Therefore, risks to pilots are assessed using the engineering control (enclosed cockpits) and baseline attire (long-sleeved shirt, long pants, shoes, and socks); per the Agency's Worker Protection Standard stipulations for engineering controls, pilots are not required to wear protective gloves for the duration of the application. With this level of protection, there are no risk estimates of concern for applicators.

Table 11.1.1 Occupational Handler Non-Cancer Exposure and Risk Estimates for Fluindapyr.											
Exposure Scenario	**Crop or Target[1]**	**Level of Concern**	**Dermal Unit Exposure (µg/lb ai)[2]**	**Inhalation Unit Exposure (µg/lb ai)[2]**	**Maximum Application Rate (lb ai/A unless indicated)[3]**	**Area Treated or Amount Handled Daily (Acres unless indicated)[4]**	**Dermal**		**Inhalation**		**Total**
			Level of PPE or Engineering control *(Single Layer + Gloves unless indicated)*	**Level of PPE or Engineering control *(No respirator unless indicated)***			**Dose (mg/kg/day)[5]**	**MOE[6]**	**Dose (mg/kg/day)[7]**	**MOE[8]**	**MOE[9]**
Mixer/Loader											
Liquid, Aerial, Broadcast	Orchard/Vineyard	1,000	37.6	0.219	0.150	350	0.00485	6,200	0.000167	180,000	6,000
	Field crop, typical				0.134	350	0.00434	6,900	0.000149	200,000	6,700
	Field crop, high acreage				0.134	1,200	0.0149	2,000	0.00051	59,000	1,900
Liquid, Airblast, Broadcast	Orchard/Vineyard	1,000	37.6	0.219	0.150	40	0.000557	54,000	0.000019	1,600,000	52,000
Liquid, Chemigation, Broadcast	Orchard/Vineyard	1,000	37.6	0.219	0.150	350	0.00485	6,200	0.000167	180,000	6,000
	Field crop, typical				0.134	350	0.00434	6,900	0.000149	200,000	6,700
	Field crop, high acreage				0.134	350	0.00434	6,900	0.000149	200,000	6,700
	Greenhouse (ornamentals)				0.270	60	0.0015	20,000	0.0000514	580,000	19,000

Table 11.1.1 Occupational Handler Non-Cancer Exposure and Risk Estimates for Fluindapyr.											
Exposure Scenario	**Crop or Target[1]**	**Level of Concern**	**Dermal Unit Exposure (µg/lb ai)[2]**	**Inhalation Unit Exposure (µg/lb ai)[2]**	**Maximum Application Rate (lb ai/A unless indicated)[3]**	**Area Treated or Amount Handled Daily (Acres unless indicated)[4]**	**Dermal**		**Inhalation**		**Total**
			Level of PPE or Engineering control *(Single Layer + Gloves unless indicated)*	**Level of PPE or Engineering control *(No respirator unless indicated)***			**Dose (mg/kg/day)[5]**	**MOE[6]**	**Dose (mg/kg/day)[7]**	**MOE[8]**	**MOE[9]**
Liquid, Groundboom, Broadcast	Landscaping, turf (commercial lawns)	1,000	37.6	0.219	0.270	5	0.000125	240,000	0.00000429	7,000,000	230,000
	Golf course (fairways, tees, greens)				0.270	40	0.001	30,000	0.0000343	870,000	29,000
	Field-grown ornamental crops				0.270	40	0.001	30,000	0.0000343	870,000	29,000
	Greenhouse (ornamentals)				0.270	60	0.0015	20,000	0.0000514	580,000	19,000
	Orchard/Vineyard				0.150	40	0.000557	54,000	0.000019	1,600,000	52,000
	Field crop, typical				0.134	80	0.000993	30,000	0.0000341	880,000	29,000
	Field crop, high-acreage				0.134	200	0.00249	12,000	0.0000851	350,000	12,000
Applicator											
Spray (all starting formulations), Aerial, Broadcast	Orchard/Vineyard	1,000	2.08 (EC)[10]	0.0049 (EC)[10]	0.150	350	0.000269	110,000	0.00000372	8,100,000	110,000
	Field crop, typical				0.134	350	0.00024	130,000	0.00000333	9,000,000	130,000
	Field crop, high-acreage				0.134	1,200	0.000823	36,000	0.0000114	2,600,000	36,000

Table 11.1.1 Occupational Handler Non-Cancer Exposure and Risk Estimates for Fluindapyr.											
Exposure Scenario	**Crop or Target[1]**	**Level of Concern**	**Dermal Unit Exposure (µg/lb ai)[2]**	**Inhalation Unit Exposure (µg/lb ai)[2]**	**Maximum Application Rate (lb ai/A unless indicated)[3]**	**Area Treated or Amount Handled Daily (Acres unless indicated)[4]**	**Dermal**		**Inhalation**		**Total**
			Level of PPE or Engineering control *(Single Layer + Gloves unless indicated)*	**Level of PPE or Engineering control *(No respirator unless indicated)***			**Dose (mg/kg/day)[5]**	**MOE[6]**	**Dose (mg/kg/day)[7]**	**MOE[8]**	**MOE[9]**
Spray (all starting formulations), Airblast, Broadcast	Orchard/Vineyard	1,000	1590	4.71	0.150	40	0.0235	1,300	0.00041	7,3000	1,300
Spray (all starting formulations), Groundboom, Broadcast	Landscaping, turf (commercial lawns)	1,000	16.1	0.34	0.270	5	0.0000535	560,000	0.00000665	4,500,000	500,000
	Golf course (fairways, tees, greens)				0.270	40	0.000429	70,000	0.0000532	560,000	62,000
	Field-grown ornamental crops				0.27	40	0.000429	70,000	0.0000532	560,000	62,000
	Greenhouse (ornamentals)				0.27	60	0.000643	47,000	0.0000799	380,000	42,000
	Orchard/Vineyard				0.150	40	0.000238	130,000	0.0000296	1,000,000	120,000
	Field crop, typical				0.134	80	0.000426	70,000	0.0000528	570,000	62,000
	Field crop, high-acreage				0.134	200	0.00106	28,000	0.000132	230,000	25,000

Table 11.1.1 Occupational Handler Non-Cancer Exposure and Risk Estimates for Fluindapyr.											
Exposure Scenario	**Crop or Target[1]**	**Level of Concern**	**Dermal Unit Exposure (µg/lb ai)[2]**	**Inhalation Unit Exposure (µg/lb ai)[2]**	**Maximum Application Rate (lb ai/A unless indicated)[3]**	**Area Treated or Amount Handled Daily (Acres unless indicated)[4]**	**Dermal**		**Inhalation**		**Total**
			Level of PPE or Engineering control *(Single Layer + Gloves unless indicated)*	**Level of PPE or Engineering control *(No respirator unless indicated)***			**Dose (mg/kg/day)[5]**	**MOE[6]**	**Dose (mg/kg/day)[7]**	**MOE[8]**	**MOE[9]**
Flagger											
Spray (all starting formulations), Aerial, Broadcast	Orchard/Vineyard	1,000	12	0.202	0.150	350	0.00155	19,000	0.000154	190,000	17,000
	Field crop, typical				0.134	350	0.00139	22,000	0.000137	220,000	20,000
	Field crop, high-acreage				0.134	350	0.00139	22,000	0.000137	220,000	20,000
Mixer/Loader/Applicator											
Liquid, Backpack, Broadcast (foliar)	Greenhouse (ornamentals)	1,000	11,200	140	0.0027 lb ai/gal	7 gal	0.000522	57,000	0.0000384	780,000	53,000
	Landscaping, trees/shrubs/bushes		30,500	69.1	0.0027 lb ai/gal	40 gal	0.00811	3,700	0.000108	280,000	3,700
	Landscaping, plants/flowers				0.0027 lb ai/gal	40 gal	0.00811	3,700	0.000108	280,000	3,700
	Landscaping, turf (commercial lawns)				0.0063 lb ai/gal	40 gal	0.0189	1,600	0.000252	120,000	1,600

Table 11.1.1 Occupational Handler Non-Cancer Exposure and Risk Estimates for Fluindapyr.

Exposure Scenario	Crop or Target[1]	Level of Concern	Dermal Unit Exposure (µg/lb ai)[2]	Inhalation Unit Exposure (µg/lb ai)[2]	Maximum Application Rate (lb ai/A unless indicated)[3]	Area Treated or Amount Handled Daily (Acres unless indicated)[4]	Dermal		Inhalation		Total
			Level of PPE or Engineering control *(Single Layer + Gloves unless indicated)*	Level of PPE or Engineering control *(No respirator unless indicated)*			Dose (mg/kg/day)[5]	MOE[6]	Dose (mg/kg/day)[7]	MOE[8]	MOE[9]
Liquid, Manually-pressurized Handwand, Broadcast (foliar)	Greenhouse (ornamentals)	1,000	430	23.6	0.0027 lb ai/gal	7 gal	0.00002	1,500,000	6.46E-06	4,600,000	1,100,000
	Landscaping, trees/shrubs/bushes				0.0027 lb ai/gal	40 gal	1.14E-04	260,000	3.70E-05	810,000	200,000
	Landscaping, plants/flowers				0.0027 lb ai/gal	40 gal	0.000114	260,000	0.000037	810,000	200,000
	Landscaping, turf (commercial lawns)				0.0063 lb ai/gal	40 gal	0.000266	110,000	0.0000862	350,000	84,000
Liquid, Mechanically-pressurized Handgun, Broadcast (foliar)	Greenhouse (ornamentals)	1,000	2,990 (DL/G)[11]	448	0.0027 lb ai/gal	175 gal	0.00347	8,600	0.00307	9,800	4,600
Liquid, Mechanically-pressurized Handgun, Broadcast	Golf course (fairways, tees, greens)		450 (DL/G)[11]	1.9	0.27	5	0.0015	20,000	0.0000372	810,000	20,000
Liquid, Mechanically-pressurized Handgun, Broadcast (foliar)	Landscaping, trees/shrubs/bushes		1360 (DL/G)[11]	8.68	0.0027 lb ai/gal	1000 gal	0.00904	3,300	0.000339	88,000	3,200

Table 11.1.1 Occupational Handler Non-Cancer Exposure and Risk Estimates for Fluindapyr.											
Exposure Scenario	**Crop or Target[1]**	**Level of Concern**	**Dermal Unit Exposure (µg/lb ai)[2]**	**Inhalation Unit Exposure (µg/lb ai)[2]**	**Maximum Application Rate (lb ai/A unless indicated)[3]**	**Area Treated or Amount Handled Daily (Acres unless indicated)[4]**	**Dermal**		**Inhalation**		**Total**
			Level of PPE or Engineering control *(Single Layer + Gloves unless indicated)*	**Level of PPE or Engineering control *(No respirator unless indicated)***			**Dose (mg/kg/day)[5]**	**MOE[6]**	**Dose (mg/kg/day)[7]**	**MOE[8]**	**MOE[9]**
Liquid, Mechanically-pressurized Handgun, Broadcast	Landscaping, turf (commercial lawns)		450 (DL/G)[11]	1.9	0.27	5	0.0015	20,000	0.0000372	810,000	20,000

1 Field crop, typical = sweet corn; field crop, high acreage = cereal grains other than sweet corn (e.g. barley, sorghum, wheat, field and pop corn) and soybean; orchard/vineyard = tree nuts
2 Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data); Level of PPE: Baseline attire (long pants, socks, shoes, and long-sleeved shirt), PPE (SL/G = baseline attire + addition of chemical resistant gloves), Engineering Controls.
3 Based on proposed labels (See Table 3.3.1).
4 Exposure Science Advisory Council Policy #9.1.
5 Dermal Dose = Dermal Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A or gal/day) × DAF (17%) ÷ BW (69 kg).
6 Dermal MOE = Dermal NOAEL (30 mg/kg/day) ÷ Dermal Dose (mg/kg/day).
7 Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A or gal/day) ÷ BW (69 kg).
8 Inhalation MOE = Inhalation NOAEL (30 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).
9 Total MOE = NOAEL (30 mg/kg/day) ÷ (Dermal Dose + Inhalation Dose)
10 EC = Engineering Control
11 DL/G = baseline attire + double layer torso + chemical resistant gloves

11.2 Short-/ Intermediate- Term Postapplication Exposure and Risk Estimates

11.2.1 Dermal PostApplication Exposure and Risk Estimates

There is the potential for occupational postapplication dermal exposure for workers performing activities in agricultural crops that have been previously treated with fluindapyr.

Occupational Postapplication Dermal Exposure Data and Assumptions
A series of assumptions and exposure factors served as the basis for completing the occupational postapplication risk assessments. Each assumption and factor and the algorithms used to estimate non-cancer exposure and dose for occupational postapplication workers is detailed in the occupational and residential exposure and risk assessment conducted for this action (Bacon, L.,Lang, E. D455860, 10/27/2020).

Dislodgeable Foliar Residue (DFR)

Chemical specific DFR data were not submitted for fluindapyr.

In accordance with 40 CFR part 158, DFR data are required for all occupational (e.g., crop, nursery, greenhouse use sites) or residential (e.g., ornamental and vegetable gardens, pick your own farms, retail tree farms) uses that could result in postapplication exposure to foliage. In the absence of chemical specific DFR data, EPA uses default values. The *2012 Standard Operating Procedures for Residential Pesticide Exposure Assessment* includes an analysis of a number of DFR studies, which resulted in the selection of a revised default values for the fraction of the application rate available for transfer after a foliar application (F_{AR}). These values are based on an analysis of 19 DFR studies. Since that time, the Agricultural Re-entry Task Force has submitted information (MRID 49299201) that corrects an application rate error made in the original submission of "ARF039 – Determination of Dermal and Inhalation Exposure to Reentry Workers During Chrysanthemum Pinching in a Greenhouse" (EPA MRID 45344501). As a result, the range of F_{AR} values was revised from 2% - 89% to 2% - 47%. In the data, a large range of transferability is observed and this variability can potentially be attributable to many factors such as active ingredient; formulation; field conditions in the studies; weather conditions (e.g., humidity); or many other difficult to quantify factors. Although witnessed across multiple chemicals, this range in F_{AR} values is not expected when considering DFR data for a single chemical. At this time, the ARTF submission did not alter the selection of 25% as the reasonable, high-end default value. Because DFR data are not available for fluindapyr, EPA is using the default value of 25%. Although there may be a small degree of uncertainty in the use of the default DFR value for fluindapyr (i.e., there is a small chance that the F_{AR} value may exceed the applicable default value), it is likely that the health-protective aspects of EPA's residential and occupational postapplication assessment methodology will more than compensate for this potential uncertainty. For example, when assessing residential and occupational postapplication exposure to gardens and ornamentals, EPA assumes the following: exposures occur to zero-day (i.e., day of application) residues every day of the assessed exposure duration (i.e., EPA assumes that no dissipation or degradation occurs, it doesn't rain, etc); individuals perform the same postapplication activities performed in the transfer coefficient study day after day (e.g., weeding, harvesting, pruning, etc.); and individuals engage in these postapplication activities for a high-

end amount of time every day (represented by data reflecting time spent gardening based on survey data).

Given the conservatisms discussed above and the potential compounding nature of these conservatisms, EPA is able to rely upon the calculated exposure estimates with confidence that exposure is not being underestimated.

HED estimates indicate that the occupational agricultural postapplication exposure for workers using default DFR values for fluindapyr is minimal in comparison to the LOC. That is, the lowest calculated MOE for occupational postapplication workers (MOE = 2000 – detasseling and hand harvesting for sweetcorn) is greater than 2x the LOC (LOC = 1000). In this instance, it is unlikely that chemical specific DFR data would be needed to further refine the exposure assessments or would add appreciably to our overall understanding of the availability of dislodgeable foliar pesticide residues for fluindapyr. Consequently, EPA is waiving the 40 CFR DFR data requirement at this time.

Turf Transferable Residue (TTR)

Chemical specific TTR data were not submitted for fluindapyr.

In accordance with 40 CFR part 158, TTR data are required for all occupational (e.g., sod farms, golf courses, parks, and recreational areas) or residential turf uses that could result in postapplication exposure to turf. In the absence of chemical specific TTR data, EPA uses default values. The *2012 Standard Operating Procedures for Residential Pesticide Exposure Assessment* includes an analysis of all TTR data, available at the time, which resulted in the selection of revised liquid and granular default values for the fraction of the application rate available for transfer after a turf application (F_{AR}). These values are based on an analysis of 59 TTR studies performed with the Modified California Roller Method (36 studies using liquids, 11 studies using wettable powders/water dispersible granules, and 12 studies using granules). The liquid results (N=131) indicate a range of F_{AR} values from 0.0005% to 6.1% and the granular results (N=37) indicate a range of 0.00064% to 0.69%. In both the liquid and granular data, a large range of transferability is observed and this variability can potentially be attributable to many factors such as active ingredient; formulation; field conditions in the studies; weather conditions (e.g., humidity); or many other difficult to quantify factors. Although witnessed across multiple chemicals, this range in F_{AR} values is not expected when considering TTR data for a single chemical. HED selected 1% and 0.2% as high-end default values for liquid and granular products, respectively. Because TTR data are not available for fluindapyr, EPA is using the default value of 1% for liquid products. Although there may be a small degree of uncertainty in the use of the default TTR value for fluindapyr (i.e., there is a small chance that the F_{AR} value may exceed the applicable default value), it is likely that the health-protective aspects of EPA's residential and occupational postapplication turf assessment methodology will more than compensate for this potential uncertainty (i.e., the methodology is likely to overestimate exposure by a factor greater than the factor than the highest measured F_{AR} values exceed the defaults). For example, when assessing residential postapplication turf exposure, EPA assumes the following: exposures occur to zero-day (i.e., day of application) residues every day of the assessed exposure duration (i.e., EPA assumes that no dissipation or degradation occurs, it

doesn't rain, the grass is not mowed, etc); individuals perform the same postapplication activities performed in the turf transfer coefficient study day after day (e.g., tumbling, playing on turf with toys, etc.); and individuals engage in these postapplication activities for a high-end amount of time every day that is represented by data reflecting time children spend outdoors and not specifically engaged in activities on turf, when in actuality children do not spend all of their outdoor time on turf and high-end levels of activity will not occur every day.

Given the conservatisms discussed above and the potential compounding nature of these conservatisms, EPA is able to rely upon the calculated exposure estimates with confidence that exposure is not being underestimated.

HED estimates indicate that the occupational turf postapplication exposure for golf courses using default TTR values for fluindapyr is minimal in comparison to the level of concern. That is, the calculated MOE for occupational postapplication workers (MOE = 14,000) is greater than 10 times higher than the level of concern (LOC = 1000). In this instance, it is unlikely that chemical specific TTR data would be needed to further refine the exposure assessments or would add appreciably to our overall understanding of the availability of turf transferable pesticide residues for fluindapyr. Consequently, EPA is waiving the 40 CFR TTR data requirement at this time.

Occupational Postapplication Non-Cancer Dermal Risk Estimates

All short- and intermediate-term occupational postapplication dermal MOEs are above the LOC at day 0 except for hand harvesting and detasseling sweet corn, where the MOE = 460 (LOC = 1,000). However, the MOE reaches 2,000 (2x the LOC) on Day 14 after treatment which is consistent with the proposed labeling. The proposed labels also state a 5-day REI for detasseling field corn and pop corn, however HED does not assess those activities for field or pop corn; the lowest MOE for field corn and/or pop corn is 2100 associated with handset irrigation. See Table 11.2.1.1

Table 11.2.1.1. Occupational PostApplication Exposure and Risk Estimates for Fluindapyr.								
Crop	**Crop Height**	**Foliage Density**	**Application Rate (lb ai/A)**	**Activity**	**Transfer Coefficient (cm^2/hr or gm/hr)**	**Residue (ug/cm^2 or ug/gm)[1]**	**Dose (mg/kg/day)[2]**	**MOE[3] (LOC =1,000)**
					Day after Treatment (Day 0; except as indicated)			
Almond	HIGH	FULL	0.150	Orchard maintenance, poling	100	0.42	0.001	36,000
Almond	HIGH	FULL	0.150	Harvesting, Mechanical (shaking)	190	0.42	0.002	19,000
Almond	HIGH	FULL	0.150	Scouting	580	0.42	0.005	6,200
Almond	LOW	MIN	0.150	Transplanting	230	0.42	0.002	16,000
Barley	LOW	FULL, MIN	0.134	Scouting	1,100	0.38	0.008	3,700
Corn, field; corn, pop; corn, sweet, grain; corn, sweet, processing	LOW/ HIGH	FULL, MIN	0.134	Irrigation (hand set)	1,900	0.38	0.014	2,100
Corn, field; corn, pop; corn, sweet, grain; corn, sweet, processing	LOW	MIN, FULL	0.134	Scouting	210	0.38	0.002	19,000
Corn, field; corn, pop; corn, sweet, grain; corn, sweet, processing	LOW	MIN, FULL	0.134	Weeding, Hand	70	0.38	0.001	58,000

Table 11.2.1.1. Occupational PostApplication Exposure and Risk Estimates for Fluindapyr.								
Crop	**Crop Height**	**Foliage Density**	**Application Rate (lb ai/A)**	**Activity**	**Transfer Coefficient (cm^2/hr or gm/hr)**	**Residue (ug/cm^2 or ug/gm)[1]**	**Dose (mg/kg/day)[2]**	**MOE[3] (LOC =1,000)**
					Day after Treatment (Day 0; except as indicated)			
Corn, pop; corn, sweet, grain; corn, sweet, processing	HIGH	FULL	0.134	Scouting	1,100	0.38	0.008	3,700
Corn, sweet, grain	HIGH	FULL	0.134	De-tasseling, hand; or Harvesting, hand	8,800	0.38	0.061	**460[4]**
						0.065 (Day 14)	0.015 (Day 14)	2,000[4] (Day 14)
Golf Course	LOW	FULL	0.27	Maintenance	3,700	0.030	0.002	14,000
Macadamia nut	HIGH	FULL	0.150	Pruning, Hand; Scouting	580	0.42	0.005	6,200
Macadamia nut	HIGH	FULL	0.150	Orchard maintenance	100	0.42	0.001	36,000
Macadamia nut	LOW	MIN	0.150	Transplanting	230	0.42	0.002	16,000
Macadamia nut	HIGH	FULL	0.150	Harvesting, Mechanical (shaking)	190	0.42	0.002	19,000
Greenhouse Crop (Ornamentals, Non-bearing Plants)	HIGH, LOW	FULL, MIN	0.27	Harvesting, Hand; Pruning, Hand; Scouting; Container Moving; Weeding, Hand; Transplanting; Grafting; Pinching; Tying/Training	230	0.76	0.003	8,700
Pecan	HIGH	FULL	0.150	Harvesting, Mechanical (shaking)	190	0.42	0.002	19,000
Pecan	HIGH	FULL	0.150	Poling; Orchard maintenance; Weeding, Hand	100	0.42	0.001	36,000
Pecan	HIGH	FULL	0.150	Pruning, Hand; Scouting	580	0.42	0.005	6,200

Table 11.2.1.1. Occupational PostApplication Exposure and Risk Estimates for Fluindapyr.								
Crop	**Crop Height**	**Foliage Density**	**Application Rate (lb ai/A)**	**Activity**	**Transfer Coefficient (cm^2/hr or gm/hr)**	**Residue (ug/cm^2 or ug/gm)[1]**	**Dose (mg/kg/day)[2]**	**MOE[3] (LOC =1,000)**
					Day after Treatment (Day 0; except as indicated)			
Pecan	LOW	MIN	0.150	Transplanting	230	0.42	0.002	16,000
Golf Course	LOW	FULL	0.27	Maintenance, greens only	2,500	0.030	0.001	20,000
Soybean	LOW	FULL, MIN	0.134	Scouting	1,100	0.32	0.007	4,400
Soybean	LOW	FULL	0.134	Weeding, Hand	70	0.32	0.0004	69,000
Walnut, English	HIGH	FULL	0.150	Harvesting, Mechanical (shaking)	190	0.42	0.002	19,000
Walnut, English	HIGH	FULL	0.150	Orchard maintenance; Poling	100	0.42	0.001	36,000
Walnut, English	HIGH	FULL	0.150	Scouting	580	0.42	0.005	6,200
Walnut, English	HIGH	FULL	0.150	Weeding, Hand	100	0.42	0.001	36,000
Walnut, English	LOW	MIN	0.150	Transplanting	230	0.42	0.002	16,000
Wheat	LOW	FULL, MIN	0.134	Scouting	1,100	0.38	0.008	3,700
Wheat	LOW	MIN, FULL	0.134	Weeding, Hand	70	0.38	0.001	58,000

1 Residue Calculations: DFR = Application Rate (lb ai/A) × F × $(1\text{-}D)^t$ × 4.54E8 µg/lb × 2.47E-8 acre/cm^2; where F = 0.25 and D = 0.10 per day; TTR = Application Rate (lb ai/A) × F × $(1\text{-}D)^t$ × 4.54E8 µg/lb × 2.47E-8 acre/cm^2; where F = 0.1 and D = 0.10 per day

2 Daily Dermal Dose = [DFR (µg/cm^2) × Transfer Coefficient × 0.001 mg/µg × 8 hrs/day × dermal absorption (17 %)] ÷ BW (69 kg).

3 MOE = POD (mg/kg/day) / Daily Dermal Dose.

4 REI stated on label is 14 days for hand harvesting and hand detasseling of sweet corn

Restricted Entry Interval
Fluindapyr exhibited low acute toxicity with oral, dermal, and inhalation dosing resulting in Toxicity Category III for oral and dermal routes of exposure and IV for inhalation route of exposure. It was not an eye or dermal irritant, but it produced moderate skin sensitization with local lymph node assay. Short- and intermediate-term postapplication risk estimates were not a concern on day 0 (12 hours following application) for most activities. However, there were risk estimates of concern related to certain activities for sweet corn (detasseling and hand harvesting) using the HED default assumptions. Estimates of risk were not of concern when the label specified REI was assumed (i.e., 14 days, where the MOE = 2,000).

11.2.2 Inhalation PostApplication Risk Estimates

There are multiple potential sources of postapplication inhalation exposure to individuals performing postapplication activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and/or particulates that contain pesticides. The agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-0687-0037). The agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (https://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219). During Registration Review, the agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for fluindapyr.

In addition, the Agency is continuing to evaluate the available postapplication inhalation exposure data generated by the ARTF. Given these two efforts, the Agency will continue to identify the need for and, subsequently, the way to incorporate occupational postapplication inhalation exposure into the agency's risk assessments.

Although a quantitative occupational postapplication inhalation exposure assessment was not performed, an inhalation exposure assessment was performed for occupational/commercial handlers. Handler exposure resulting from application of pesticides outdoors is likely to result in higher exposure than postapplication exposure. Therefore, it is expected that these handler inhalation exposure estimates would be protective of most occupational postapplication inhalation exposure scenarios; handler exposures are not of concern.

12.0 References

Bacon, L., Lang, E., 10/27/2020, D455860, Fluindapyr. Occupational and Residential Exposure Assessment for Proposed Uses of the New Active Ingredient.

Camp, J., TXR.0057980, 12/04/2019. Fluindapyr. Summary of Hazard and Science Policy Council (HASPOC) Meeting on November 26, 2019: Recommendations on the Need for an Immunotoxicity Study, Dermal Toxicity Study, and a Comparative Thyroid Assay.

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Negussie, M., D454238, 11/13/2019, D. Fluindapyr. Report of the Residues of Concern Knowledgebase Subcommittee (ROCKS).

Engel P., D447798, 06/18/2020. Fluindapyr: Drinking Water Assessment (DWA) for the Proposed New Chemical Registration

McGovern R., D454240, 10/27/2020. Fluindapyr. Acute and Chronic Aggregate Dietary Exposure and Risk Assessments

McGovern R., D454241, 10/27/2020. Fluindapyr Summary of Analytical Chemistry and Residue Data

Appendix A. Toxicology Profile and Executive Summaries

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.340) for fluindapyr are in Table A.1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table A.1 Toxicology Data Requirements for fluindapyr

Test	Technical	
	Required	Satisfied
870.1100 Acute Oral Toxicity	yes	yes
870.1200 Acute Dermal Toxicity	yes	yes
870.1300 Acute Inhalation Toxicity	yes	yes
870.2400 Primary Eye Irritation	yes	yes
870.2500 Primary Dermal Irritation	yes	yes
870.2600 Dermal Sensitization	yes	yes
870.3100 Oral Subchronic (rodent)	yes	Yes
870.3150 Oral Subchronic (nonrodent)	yes	yes
870.3200 21-Day Dermal	yes	waived[a]
870.3250 90-Day Dermal	CR	
870.3465 90-Day Inhalation (28-day inhalation)	yes	yes
870.3700a Developmental Toxicity (rodent)	yes	yes
870.3700b Developmental Toxicity (nonrodent)	yes	yes
870.3800 Reproduction	yes	yes
870.4100 Combined Chronic Toxicity/carcinogenicity (rat) 870.4100b Chronic Toxicity (nonrodent)	yes	yes
870.4200b Oncogenicity (mouse)	no	yes
	yes	yes
870.5100 Mutagenicity—Gene Mutation – bacterial	yes	yes
870.5300 Mutagenicity—Gene Mutation - mammalian 870.5xxx Mutagenicity—Structural Chromosomal Aberrations 870.5xxx Mutagenicity—Other Genotoxic Effects	yes	yes
	yes	yes
870.6100a Acute Delayed Neurotox. (hen)	no	—
870.6100b 90-Day Neurotoxicity (hen)	no	—
870.6200a Acute Neurotox. Screening Battery (rat)	yes	yes
870.6200b 90-Day Neuro. Screening Battery (rat)	yes	yes
870.6300 Develop. Neuro	CR	
870.7485 General Metabolism	yes	yes
870.7600 Dermal Penetration	no	yes
870.7800 Immunotoxicity	yes	waived[a]

[a]: The requirement of the study was waived (Camp, J., TXR 0057980, 12/04/2019).

A.2 Toxicity Profiles

Fluindapyr: Toxicity Profile

A.2.1. Summary of Acute Toxicity Data for Fluindapyr (Technical ai)				
Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute oral LD_{50} - rat	50518084	LD_{50} > 2000 mg/kg (F)	III
870.1200	Acute dermal LD_{50} - rat	50518085	LD_{50} > 2000 mg/kg (M & F)	III
870.1300	Acute inhalation LC_{50} - rat	50518086	LC_{50} > 5.2 mg/L (M & F)	IV*
870.2400	Acute eye irritation – rabbit	50518087	Non-irritating	IV
870.2500	Acute dermal irritation – rabbit	50518088	Non-irritating	IV
870.2600	Skin sensitization - mouse (LLNA)	50518089	Moderately sensitizing+	NA

*: Treated rats showed signs of ↑ respiratory rate, hunched posture, ataxia, & piloerection.
+: SI values: 1.97, 3.44, 5.46 for 10, 25, and 50% (w/w), respectively

Table A.2.2 Subchronic, Chronic and Other Toxicity Studies			
Guideline No	Study Type	MRID No. (Year)/ Classification /Doses	Results
Subchronic Toxicity Studies			
870.3050	28-Dayoral toxicity study – rats (dietary)	50518091 (2016) Acceptable/non-guideline 0, 300, 1000, 2000, & 4000 ppm M: 0, 24, 84, 166, & 320 mg/kg/day; F: 0, 27, 85, 172, & 324 mg/kg/day	NOAEL = 320/324 mg/kg/day (M/F) (HDT). No adverse effects were seen at any tested doses. LOAEL = cannot be established.
	28-Day oral toxicity study-mice (dietary)	50518092 (2016) Acceptable/non-guideline 0, 300, 1000, 3000, & 5000 ppm M 0, 61, 192, 528, & 1093 mg/kg/day F: 0, 71, 275, 675, & 1339 mg/kg/day	NOAEL = 1093/1339 mg/kg/day (M/F) (HDT). No adverse effects were seen at any tested doses. LOAEL = cannot be established.

870.3100	90-day oral toxicity study – rats (dietary)	50518093 (2016) Acceptable/guideline 0, 100, 450, or 2000/6000 (males: after 28 days raised to 6000 ppm; females remained at 2000 ppm for the entire duration.) M: 0, 6, 24, & 330 mg/kg/day F: 0, 7, 30, & 139 mg/kg/day	NOAEL = 330/139mg/kg/day (M/F) (HDT). No adverse effects were found. LOAEL = cannot be established.
	90-day oral toxicity study – mice. (dietary)	50518094 (2016) Acceptable /guideline 0, 300, 1000, and 3000 ppm M:0, 51, 162, and 529 mg/kg/day F: 0, 80, 274, & 799 mg/kg/day	NOAEL = 529/799 mg/kg/day (M/F) HDT. No adverse effects were seen at any dose levels. LOAEL = cannot be established.
	90-day oral toxicity in dogs (Capsule)	50518096 (2016) Acceptable/guideline 0, 10, 40, & 200 mg/kg/day 50518095(2016) 28-dayrange-findingstudy (capsule) 0, 20, 70, 200,&500 mg/kg/day	NOAEL = 40 mg/kg/day (M/F). LOAEL = 200 mg/kg/day (M/F) based on adverse liver effects which included hepatocellular hypertrophy, increased liver weights, bile duct hyperplasia, and correlated clinical pathology changes in ALP, ALT, GGT, and cholesterol. The range finding study results indicated adverse effects in the liver at 500 mg/kg/day (↑liver weights, hepatocellular hypertrophy with correlated increases in ALP, ALT, & SDH).

Subchronic, Chronic and Other Toxicity Studies

Guideline No	Study Type	MRID No. (Year)/ Classification /Doses	Results
870.3200	28-Day Dermal in Rats	50518097 (2015) Unacceptable 0, 100, 300 and 1000 mg/kg/day	No adverse effect was found. NOAEL was 1000 mg/kg/day (highest dose tested, HDT). Unacceptable as the application method consisted of placing the test material on a piece of gauze (without moistened it) and applied onto the application site. This method would have influenced the outcome of the study, and it was considered as a major deficiency.

870.3465	28-Day inhalation toxicity (Nose only; 6 hours/day)	50518101 (2016) Acceptable/guideline 0, 0.06, 0.30, or 0.98 mg/L. 50518099 (2016) 5-Day inhalation study 0, 0.1, 0.43, or 1.55 mg/L Nose only; 6 hrs/day (3 rats/sex/concentration	NOAEC = 0.98 mg/L (highest concentration tested and approximately the limit concentration for an inhalation study). LOAEC = cannot be established.
Developmental and Reproductive Toxicity Studies			
870.3700a	Prenatal Developmental Toxicity Study in Rats (gavage)	50518105 (2015) Acceptable/guideline 0, 60, 300, & 1000 mg/kg/day 50518103 Range-finding study	Maternal: NOAEL= 1000 mg/kg (HDT) as no adverse effects were found. LOAEL = cannot be established. Developmental NOAEL = 1000 mg/kg (HDT) No adverse developmental effects were seen.
870.3700b	Prenatal Developmental Toxicity Study in Rabbits (gavage)	50518106 (2015) (Acceptable/guideline 0, 50, 250, & 750 mg/kg/day 50518104 Range-finding study	Maternal: NOAEL = 750 mg/kg (HDT). LOAEL = cannot be established. Developmental NOAEL = 750 mg/kg (HDT); no adverse developmental effects were found.

Subchronic, Chronic and Other Toxicity Studies			
Guideline No	Study Type	MRID No. (Year)/ Classification /Doses	Results
870.3800	two Generation Reproduction - rats (diet)	50518108 (2015) Acceptable/guideline 0, 100, 400, or 3200/1600 ppm (M: 0, 6, 25, or 142 mg/kg/day F: 0, 8, 30, or 173 mg/kg/day) 50518107 (2014) Preliminary reproduction. study 0, 400,12000, 4000 or 12000 ppm (0, 30, 100, 300, or 1000 mg/kg/day)	Parental: NOAEL = 25/30 mg/kg/day (M/F). LOAEL = 142/173 mg/kg/day(M/F) based on ↑incidence of thyroid follicular hypertrophy/hyperplasia. Note: some of adverse effects stated as the reproductive endpoints might also be applicable as the parental effects. Offspring: NOAEL = 25/30 mg/kg/day (M/F). LOAEL = 142/173 mg/kg/day (M/F) based on ↓F1 & F2 pup body weights (↓11% in males &; ↓13% in females) and decreased thymus and spleen weights (both absolute and relative to brain weight) in the F1 and F2 pups. Reproductive: NOAEL = 25/30 mg/kg/day (M/F). LOAEL = 142/173 mg/kg/day based on corpora lutea vacuolation, increase epithelial mucification, increase anestrous epithelium of the vagina, delayed vaginal opening, increase in acyclic cycles (with corresponding decrease in regular cycles), decrease in antral follicle counts, increase in seminal vesicle weight, decreases in ovary and uterine weights, and attenuated endometrium.
Chronic Toxicity Studies			
870.4100 /4200a	Chronic tox/ carcinogenicity study rats	50518111 (2017) Acceptable/guideline M: 0, 100, 400, 1600 and 4800 ppm (0, 4, 17, 67, and 202 mg/kg/day) F: 0, 100, 400 and 1600 ppm (0, 5, 21, and 83 mg/kg/day)	NOAEL = 5 mg/kg/day. LOAEL = 21 mg/kg/day based on increased incidence of uterine endometrial hyperplasia. No increase in tumor incidence was seen.
870.4100b	1-Year Oral Toxicity Study in Dogs (capsule)	50518110 (2017) Acceptable/guideline M: 0, 4, 8, 40, and 100 mg/kg/day. F: 0, 2, 8, and 40 mg/kg/day	NOAEL = 4 mg/kg/day. LOAEL = 8 mg/kg/day based on decreased body weights (↓10-15%).

870.4200b	Carcinogenicity study-mice (78 weeks)	50518109 (2017) Acceptable / guideline 0, 100, 500 or 3000 ppm M: 0, 14, 67, or 412 mg/kg/day F: 0, 18, 84, or 538 mg/kg/day	NOAEL = 67 mg/kg/day (M). LOAEL = 412 mg/kg/day based on increases in liver weights and in the incidence of foci of hepatocellular alterations (basophilic, eosinophilic, vacuolation, necrosis, and pigmented macrophages. For females, the NOAEL = 538 mg/kg/day (HDT) as no adverse effect was found in females. Slightly increased incidence of hepatocellular adenomas was seen in males only at 412 mg/kg/day.
Genotoxicity Studies			
Guideline No	Study Type	MRID No. (Year)/ Classification /Doses	Results
870.5100	Bacterial Reverse Mutation Test (*S. typhimurium:* TA98, TA100, TA1535, TA1537) and *E. coli*)	50518112 (2013) Acceptable/guideline Plate incorporation test: 3-5000 µg/plate (+/- S9) Pre-incubation test: 10- 5000 µg/plate (+/- S9)	**Negative** 3-5000 µg/plate (+/- S9). Precipitation occurred at 333-5000 µg/plate. Positive controls: +S9: 2-aminoanthracene -S9: Sodium azide, 4-Nitro-*O*o-phenylene-diamine, and methyl methane sulfonate.
	Bacterial Reverse Mutation Test (*S. typhimurium:* TA98, TA100, TA1535, TA1537, & TA102)	50518250 (2017) Acceptable/guideline Plate incorporation & Pre-incubation tests: 10- 5000 µg/plate (+/- S9)	**Negative** Positive controls: +S9: 2-aminoanthracene. -S9: Sodium azide, 4-Nitro-*O*o-phenylene-diamine, and methyl methane sulfonate.
870.5300	*In Vitro* Mammalian Cell Gene Mutation Test [mouse lymphoma cess at TK$^{+/-}$ locus]	50518113 (2014) Acceptable/guideline Solvent: DMSO Positive control: +S9: cyclophosphamide -S9: methyl methane sulfonate	**Negative** Gene mutation at the TK$^{+/-}$locus in L5178Y mouse lymphoma cells. Experiment I: 4 hr exposure to 3.5 to 112 µg/mL (-S9) 4 hr exposure to 3.9 to 84 µg/mL (+S9) Precipitation at $\geq$56 µg/mL (+/- S9) Experiment II: 4 hr exposure to 0.2 to 6 µg/mL (- S9) 4 hr exposure to 3.9 to 84 µg/mL (+S9).
870.5375	*In Vitro* Mammalian Chromosome Aberration Test with human lymphocyte cultures	50518114 (2014) Acceptable /guideline Solvent:DMSO Positive control: +S9: cyclophosphamide -S9: ethylmethane sulfonate	**Negative** Human lymphocyte cultures were exposed as follows: treatment method (+/- S9) and a continuous treatment method (-S9). Pulse Method: Experiment I. 4 hrs exposure w/18 hrs recovery (+/- S9)to 23.6-3635 µg/mL. Experiment II: 22 hrs continuous exposure (-S9) to 7.7 - 3650 µg/ml Experiment IIB: 4 hrs exposure with/18hrs recovery (+S9) to 25 - 600 µg/mL

870.5395	(Other Genotoxic Effects) *In vivo* Mouse bone marrow micronucleus *(gavage)(NMRI mice: 7 males/time point)*	50518115 (2014) Acceptable/guideline Vehicle control: 0.5% carboxymethylcellulose Positive control: cyclophosphamide (40 mg/kg in sterile water, gavage)	**Negative** 7 males NMRI mice/time point were administer (gavage) at 2000 mg/kg in 0.5% carboxymethylcellulose and test animals were sac. at 24 or 48 hrs postdosing. No clinical signs of toxicity were found.
	In-vivo micronucleus assay in mouse peripheral blood of NMRI mice (5/sex/dose) (gavage)	50518251 (2018) Acceptable/guideline Vehicle control: cotton seed oil. Positive control: Cyclophosphamide (40 mg/kg in saline with ip injection)	**Negative** 5 mice/sex/dose group were administered (gavage) fluindapyr in cotton seed oil at 0, 250, 500. 1000, or 2000 mg/kg for male and 0, 250, 500. And 1000 for females**.** Peripheral blood was collected was collected at 44 hr following the final dosing mice. At 2000 (males) and 1000 mg/kg males and females showed clinical signs including reduction in spontaneous activity prone position, constricted abdomen, bradykinesia, ataxia, hunched posture, piloerection, and eyelid/eye closed.

Neurotoxicity Studies

Guideline No	Study Type	MRID No. (Year)/ Classification /Doses	Results
870.6200a	Acute Neurotoxicity-rats (gavage) (single dose)	50518090 (2016) Acceptable/guideline Phase I: 0, 125, 500, or 2000 mg/kg Phase II: 0, 15, 30, or 60 mg/kg	NOAEL = 60 mg/kg. LOAEL = 125 mg/kg based on decreased total and ambulatory motor activities in both sexes and decreased rearing in females. It should be noted that the decreased motor activity might not indicate the neurotoxic potential of this chemical as many other neurobehavioral parameters (such as home observations, handling parameters, or neuromuscular observations) were not affected. In addition, neuropathology of both central and peripheral nerves were not observed.
870.6200b	90-Day Dietary Study –rats	50518116 ((2016) Acceptable/guideline 0, 200, 600, or 5000/2000 (M/F) ppm M: 0, 12, 34, or 296 mg/kg/day F: 0, 13, 39, or 129 mg/kg/day	NOAEL = 39 mg/kg/day (females). LOAEL = 129 mg/kg/day (females) based on decreased body weights (↓11%) and food consumption in females. No adverse effects were seen in males. NOAEL = 296 mg/kg/day (HDT).

Metabolism studies			
870.7485	Metabolism Studies –Rat. 7 metabolism studies including an *in-vitro* interspecies comparison study using rat, mouse, dog, and human hepatocytes.	MRID 50518117 (2014) Acceptable/guideline Excretory balance (urine, feces, CO_2), blood and plasma levels and tissue distribution with [^{14}Cpyrazole]-fluindapyr. MRID 50518118 (2016) Acceptable/guideline Excretory balance (urine, feces, CO_2), blood and plasma levels and tissue distribution with [^{14}Cphenyl]-fluindapyr. MRID 50518119 (2016) Acceptable/guideline Excretory balance (urine, feces), with [^{14}Cpyrazole]-fluindapyr. MRID 50518120 (2017) Acceptable/guideline Identification/characteriza-tion of metabolites (following single and repeated dosing) with [14C-phenyl]-fluindapyr. MRID 50518121 (2017) Acceptable/guideline Interspecies comparison of *in-vitro* metabolism with rat, mouse, dog, and human hepatocytes using [14C-phenyl]-fluindapyr. MRID 50518122 (2017) Acceptable/guideline Bile excretion of radioactivity experiment with [^{14}C-pyrazole]fluindapy (repeated dosing). MRID 50518123 (2018) Acceptable/guideline Identification/characteriza-tion of metabolites in bile duct cannulated rats following repeated dosing with unlabeled and [^{14}Cpyrazole]-fluindapyr.	Seven metabolism studies were conduct; 4 studies were conducted with (^{14}C-pyrazol-)-fluindapyr, while 3 ofher studies were performed with (^{14}C-phenyl)-fluindapyr. There was no significant difference in any of the metabolism parameters with either labelled compound. The results of all the metabolism studies can be summarized as follows: **Absorption**: With oral administration fluindapyr was absorbed rapidly. Much of the absorption occurred within 24 hours after dosing approximately 75% and 73% administered dose (AD) was absorbed by males and female, respective. By 48 hours postdosing, greater than 90% AD was absorbed by both males and females. The results indicated a T_{max} for plasma concentration was 2.0 and 3.0 hours (hrs) for males and females, respectively. An estimated $t_{1/2}$ for plasma concentration was approximately 5.6 and 5.2 hrs. for males and females, respectively. Plasma concentrations of fluindapy were generally similar in males and females. **Distribution**: After absorption the radioactivity was distributed to all major organs. After 2 hrs post dosing, the organs, which had the higher concentration, were liver (≈5% AD), kidneys (≈0.6 %AD), gastrointestinal tract (GI) (≈6%AD), and skin (≈3%AD). After 168 hrs postdosing, none of the tissues contained more than 0.1% AD. **Metabolism**: The absorbed fluindapyr was metabolized rapidly and extensively metabolized and at least 50 metabolites were found. Metabolism was mainly through *N*-demethylation, oxidation of methyl groups to hydroxymethyl and further to carboxylic acid. Additional metabolites, to a lesser extent, were also formed through double hydroxylation, dehydrogenation and conjugation with glucuronic acid. With bile duct cannulation study, the major metabolites (>10% applied dose in bile and urine) included 1-hydroxymethyl-fluindapyr, 1-hyroxymethyl-*N*-desmethyl-fluindapr, 1-carboxy-fluindapyr, 1-carboxy-*N*-desmethyl-fluindapyr and *N*-hydroxy-fluindapyr. *In vitro* metabolism was studied in hepatocytes of the mouse, rat, dog and humans. Overall, the results indicate that the metabolic pathways are similar across the four species. The rat was the species that metabolized fluindapyr most similarly to metabolism in humans. There were no unique metabolites found in human hepatocytes. Furthermore, the enantiomeric ratio of residual fluindapyr remained virtually unchanged indicating no enantioselective metabolism. **Elimination**: The majority of the applied dose (≈ 90%) was eliminated within 48 hours after dosing. Excretion occurred predominantly via feces (≈ 72% AD) and a smaller amount via urine (≈26% AD). Negligible amounts of radioactivity were recovered in expired air (<0.01%) or recovered from the carcass (< 0.5%). The elimination profiles of the compound in both male and female rats were similar, and essentially no bioaccumulation occurred. The unchanged parent compound elimination was similar in both genders, ranging between 5 and 15% of AD.

Subchronic, Chronic and Other Toxicity Studies			
Guideline No	Study Type	MRID No. (Year)/ Classification /Doses	Results
Dermal Absorption Studies			
870.7600	Dermal penetration MRID:50518124 (2018) Acceptable/nonguideline. In-vitro dermal penetration with human skin (3.0, 260, and 4200 µg/cm^2)		After single applications of [^{14}C-pyrazole]-fluindapyr to excised human skin sections, ≥90% of the applies dose was recovered. Much of the applied dose remained on the skin (≈ 93%, 106%, and 96% of the applied dose for 4200, 260, and 3.0 µg/cm^2 groups, respectively). The dislodgeable dose (skin wash, donor chamber, and tape strips 1-2) for the 4200, 260, and 3.0 µg/cm^2 groups accounted for approximately 94%, 106%, and 97% of the dose, respectively. **Potentially absorbed dose (receptor fluid, receptor chamber wash, skin, and stratum corneum [tape strips 3-20]) was only 0.14%, 0.71%, and 2.99% of the applied dose for 4200, 260, and 3.0 µg/cm^2, respectively**. These results demonstrated that *in vitro* percutaneous absorption of an SC concentrate and two aqueous dilutions of [^{14}C]-fluindapyr was minimal with human skin membranes.
Immunotoxicity Studies			
870.7800	28-Day Immunotoxicity		Data waiver request submitted (MRID 50518126) and to be considered by HASPOC.

Appendix B. Metabolism Summary Table

Table B.1. Fluindapyr and Major Metabolites/Degradate Structures.

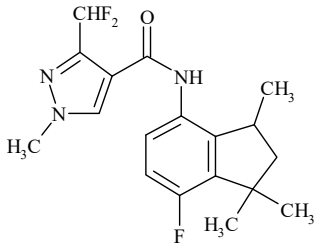
Name Structure	Major[1] Plant				Major Livestock NOR[3] Studies				Water		Rat
	Primary		Rotational		Poultry		Ruminant		Major [5]	Minor [6]	
	NOR[3]	MOR[4]	NOR[3]	MOR[4]	%TRR	ppm	%TRR	ppm			
Parent **Fluindapyr (F9990)** 	Wheat forage- 30.60-36.92% Wheat hay- 28.32-31.35% Wheat straw- 28.28-28.83% Wheat grain- 45.49-55.5% Soybean forage- 11.39-14.80% Soybean hay- 6.64-10.15% Rice straw- 46.4-49.8% Rice grain- 50.0-50.9% Sugar beet tops- 15.07-18.21% Sugar beet roots- 42.86-50.38% Grape leaves- 46.1-58.7% Grape berries- 63.5-65.3%	Almond hulls- 1.04-8.89 ppm (3.72±2.19) Almond nutmeat- <0.010-0.025 ppm (0.014±0.005) Pecan nutmeat- <0.010-0.025 ppm (0.013±0.005) Sweet corn K+CWHR- <0.010 Sweet corn forage- 0.016-6.75 ppm (1.01±1.80) Sweet corn stover- 0.166-12.7 ppm (2.00±4.28) Field corn forage- 0.050-2.63 ppm (0.907±0.681) Field corn grain- <0.010 ppm Field corn stover- <0.010-2.78 ppm (1.04±0.749) Sorghum forage- 0.238-5.11 ppm (1.72±1.86) Sorghum grain- 0.095-0.448 ppm (0.282±0.114) Sorghum stover- 0.110-1.67 ppm (0.376±0.324) Wheat forage- 0.151-11.4 ppm (3.04±2.53)			Skin with fat- 88.3-93.5% Fat- 76-94.9% Eggs- 30.8-48.2 Muscle- 37.6-38.5	Skin with fat- 0.041-0.050 Fat- 0.073-0.090 Eggs- 0.018-0.028 Muscle- 0.004-0.004	Milk fat- 75.2-93.2% Fat- 73.6-74.5% Muscle- 32.3-39.0%	Milk fat- 0.045-0.057 Fat- 0.024-0.042 Muscle- 0.004-0.006	Aerobic soil- 56.13-90.11% Anaerobic soil- 83.0-95.1% Soil photolysis- 77.92-83.03% Aqueous photolysis- 87.01-98.32% Hydrolysis- 96.4-99.7% Aerobic aquatic- 75.9-89.78%	Field studies- 0.4-9.8%	MRID 50518123: Bile- ND Urine- ND-0.56% Feces- 5.36-7.20% MRID 50518118: Brain- 0.07-0.44% Heart- 0.05-0.22% Lung- 0.07-0.28% Kidneys- 0.16-0.72% Liver- 1.24-6.70% Spleen- 0.02-0.08% GI tract- 2.33-8.60% Thyroid- ND Testes/ ovaries- 0.01-0.16% Skin- 1.06-4.91% Carcass- 74.01-86.59%

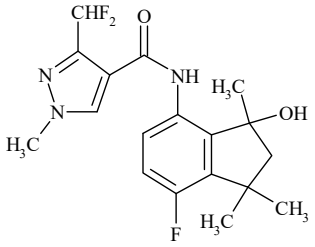
Table B.1. Fluindapyr and Major Metabolites/Degradate Structures.											
Name Structure	Major[1] Plant				Major Livestock NOR[3] Studies				Water		Rat
	Primary		Rotational		Poultry		Ruminant		Major [5]	Minor [6]	
	NOR[3]	MOR[4]	NOR[3]	MOR[4]	%TRR	ppm	%TRR	ppm			
		Wheat hay- 0.067-6.58 ppm (1.72±1.53) Wheat grain- <0.010-0.268 ppm (0.081±0.066) Wheat straw- 0.040-11.8 ppm (3.10±3.71) Wheat whole plant (14-day PHI)- 1.96-3.82 ppm (2.89±1.31) Grape- 0.109-2.21 ppm (0.611±0.520) Soybean forage- <0.010-11.5 ppm (2.87±2.62) Soybean hay- <0.010-17.7 ppm (5.34±5.38) Soybean seed- <0.010-0.198 ppm (0.025±0.032)									
3-OH-F9990 	Wheat hay- 10.27-10.60% Wheat straw- 12.30-13.56% Wheat grain- 20.35-22.08% Rice straw- 10-9-11.0% Grape leaves- 9.3-11.5% Grape berries- 11.9-15.1%	Almond hulls- 0.023-0.304 ppm (0.164±0.064) Almond nutmeat- <0.010 ppm Pecan nutmeat- <0.010 ppm Sweet corn K+CWHR- <0.010 Sweet corn forage- <0.010-1.53 ppm (0.128±0.290) Sweet corn stover- 0.017-0.236 ppm (0.067±0.073) Field corn forage-							Aerobic soil- 4.59-18.96% Anaerobic soil- 2.15-5.21% Soil photolysis- 8.43-10.43%	Aqueous photolysis- ND Hydrolysis- ND Aerobic aquatic- 3.97-4.19% Anaerobic aquatic- 4.17-5.41% Field studies-	Bile- 5.90-17.57% Urine- ND-0.75% Feces- ND

Table B.1. Fluindapyr and Major Metabolites/Degradate Structures.											
Name Structure	Major[1] Plant				Major Livestock NOR[3] Studies				Water		Rat
	Primary		Rotational		Poultry		Ruminant		Major [5]	Minor [6]	
	NOR[3]	MOR[4]	NOR[3]	MOR[4]	%TRR	ppm	%TRR	ppm			
		<0.010-0.068 ppm (0.022±0.012) Field corn grain- <0.010 ppm Field corn stover- <0.010-0.209 ppm (0.070±0.055) Sorghum forage- <0.010-0.190 ppm (0.042±0.056) Sorghum grain- <0.010-0.031 ppm (0.014±0.006) Sorghum stover- <0.010-0.260 ppm (0.048±0.054) Wheat forage- 0.011-0.352 ppm (0.075±0.075) Wheat hay- <0.010-0.319 ppm (0.099±0.091) Wheat grain- <0.010-0.017 ppm (0.010±0.002) Wheat straw- 0.010-1.69 ppm (0.357±0.479) Wheat whole plant (14-day PHI)- 0.158-0.289 ppm (0.223±0.093) Grape- <0.010-0.071 ppm (0.023±0.016) Soybean forage- <0.010-0.408 ppm (0.083±0.075) Soybean hay- <0.010-0.882 ppm								5.1-8.3%	

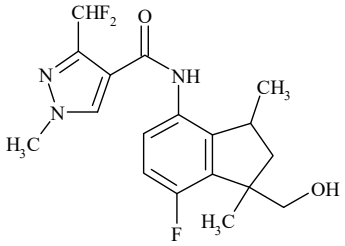
Table B.1. Fluindapyr and Major Metabolites/Degradate Structures.											
Name Structure	Major[1] Plant				Major Livestock NOR[3] Studies				Water		Rat
	Primary		Rotational		Poultry		Ruminant		Major [5]	Minor [6]	
	NOR[3]	MOR[4]	NOR[3]	MOR[4]	%TRR	ppm	%TRR	ppm			
		(0.253±0.219) Soybean seed- <0.010									
1-OH-Me-F9990 	Wheat forage- 51.54-53.67% Wheat hay- 27.23-59.81% Wheat straw- 35.20-47.68% Rice straw- 29.4-34.5% Rice grain- 24.1-28.2% Sugar beet immature tops- 17.34-18.69% Sugar beet tops- 61.95-71.25% Sugar beet root- 24.85-34.95% Grape leaves- 18.2-31.4% Grape berries- 18.3-19.6% Soybean hay- 26.44-34.04%	Almond hulls- <0.010-0.678 ppm (0.185±0.229) Almond nutmeat- <0.010 ppm Pecan nutmeat- <0.010 ppm Sweet corn K+CWHR- <0.010 ppm Sweet corn forage- 0.042-0.638 ppm (0.179±0.190) Sweet corn stover- 0.181-0.768 ppm (0.350±0.178) Field corn forage- <0.010-0.378 ppm (0.098±0.080) Field corn grain- <0.010 ppm Field corn stover- <0.010-1.18 ppm (0.263±0.252) Sorghum forage- 0.034-0.359 ppm (0.139±0.085) Sorghum grain- 0.022-0.143 ppm (0.063±0.036) Sorghum stover- 0.029-0.747 ppm (0.210±0.234) Wheat forage- 0.088-0.581 ppm (0.244±0.104) Wheat hay-			Eggs- 26.1- 31.7% Muscle- 6.4- 14.5%	Eggs- 0.015- 0.018 Muscle- 0.002- 0.002	Skim milk- 16.0- 31% Fat- 7.2- 10.6% Muscle- 34.0- 41.3% Feces- 21.7- 21.8%	Skim milk- 0.002- 0.003 Fat- 0.002- 0.006 Muscle- 0.004- 0.006 Feces- (NR[7])			Bile- 6.41- 13.44% Urine- ND- 0.95% Feces- ND

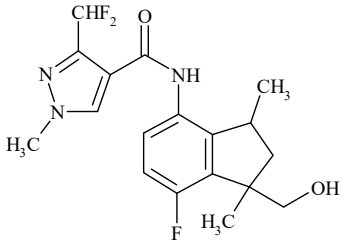
Table B.1. Fluindapyr and Major Metabolites/Degradate Structures.											
Name Structure	Major[1] Plant				Major Livestock NOR[3] Studies				Water		Rat
	Primary		Rotational		Poultry		Ruminant		Major [5]	Minor [6]	
	NOR[3]	MOR[4]	NOR[3]	MOR[4]	%TRR	ppm	%TRR	ppm			
		<0.010-1.97 ppm (0.665±0.445) Wheat grain- <0.010-0.049 ppm (0.016±0.010) Wheat straw- 0.030-1.83 ppm (0.361±0.370) Wheat whole plant (14-day PHI)- 0.471-0.747 ppm (0.609±0.195) Grape- <0.010-0.450 ppm (0.104±0.127) Soybean forage- <0.010-1.26 ppm (0.120±0.089) Soybean hay- <0.010-4.40 ppm (1.01±1.05) Soybean seed- <0.010-0.015 ppm (0.010±0.001)										
1-OH-Me-F9990 plus DM-F9990-*N*-serine 	Soybean forage- 28.35-29.62% Soybean hay- 22.33-25.53%										

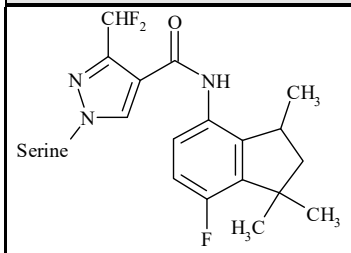
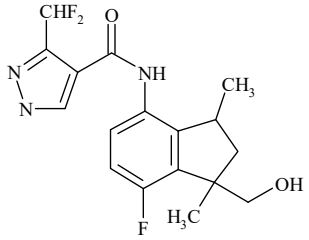
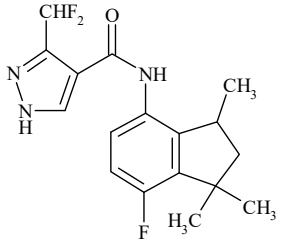
Table B.1. Fluindapyr and Major Metabolites/Degradate Structures.											
Name Structure	Major[1] Plant				Major Livestock NOR[3] Studies				Water		Rat
	Primary		Rotational		Poultry		Ruminant		Major [5]	Minor [6]	
	NOR[3]	MOR[4]	NOR[3]	MOR[4]	%TRR	ppm	%TRR	ppm			
											
1-OH-Me-DM-F9990 		Soybean forage- <0.010-0.426 ppm (0.112±0.112) Soybean hay- <0.010-0.759 ppm (0.292±0.177) Soybean seed- <0.010-0.011 ppm (0.010±0.001) Wheat whole plant (14-day PHI)- 0.073-0.083 ppm (0.078±0.007) Wheat grain- <0.010 ppm Wheat straw- 0.132-0.437 ppm (0.312±0.108)									Bile- 10.12- 26.48% Urine- 0.65-2.89% Feces- ND- 0.25%
DM-F9990 					Liver- 36- 61.1%	Liver- 0.042- 0.066					Bile- ND- 0.83% Urine- ND Feces- ND- 0.21%

Table B.1. Fluindapyr and Major Metabolites/Degradate Structures.

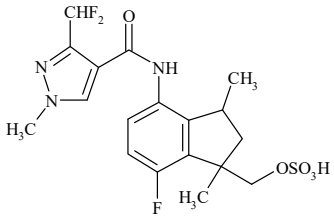
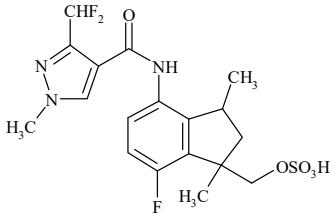
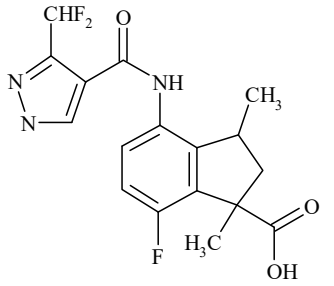
Name Structure	Major[1] Plant				Major Livestock NOR[3] Studies				Water		Rat
	Primary		Rotational		Poultry		Ruminant		Major [5]	Minor [6]	
	NOR[3]	MOR[4]	NOR[3]	MOR[4]	%TRR	ppm	%TRR	ppm			
1-SO_4-Me-F9990 					Liver- 6.8-10%	Liver- 0.008-0.009					
1-COOH-F9990 		Wheat whole plant (14-day PHI)- 0.009-0.021 ppm (0.015±0.008) Wheat grain- <0.009 ppm Wheat straw- 0.015-0.040 ppm (0.028±0.012)			Muscle- 11-12.1%	Muscle- 0.002-0.002	Liver- 12.5-14.3% Urine- 10.5-13.0% Feces- 39.2-48.7%	Liver- 0.027-0.039 Urine- (NR[7]) Feces- (NR[7])	Aerobic soil- 3.84-24.09% Anaerobic soil- 2.82-14.38% Aerobic aquatic- 10.13-10.85%	Anaerobic aquatic- 1.50-7.24% Hydrolysis- ND Field studies- 1.9-8.6%	Bile- 5.24-9.42% Urine- 1.36-1.67% Feces- ND
1-COOH-DM-F9990 											Bile- 6.05-15.13% Urine- 2.97-9.27% Feces- ND-0.39%

Table B.1. Fluindapyr and Major Metabolites/Degradate Structures.

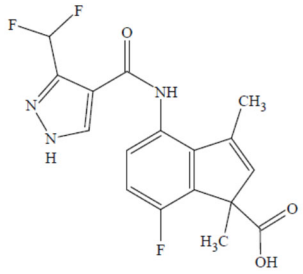
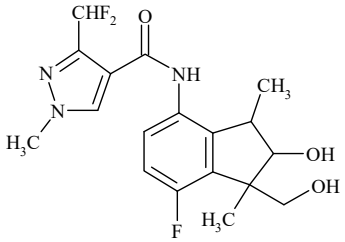
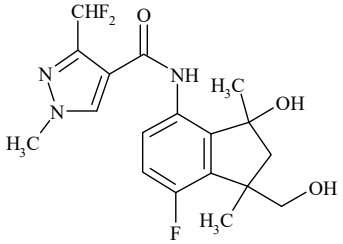
Name Structure	Major[1] Plant				Major Livestock NOR[3] Studies				Water		Rat
	Primary		Rotational		Poultry		Ruminant		Major [5]	Minor [6]	
	NOR[3]	MOR[4]	NOR[3]	MOR[4]	%TRR	ppm	%TRR	ppm			
1-COOH-deH-DM-F9990 											Bile- ND-1.49% Urine- 0.25-1.11% Feces- ND
Di-OH-F9990  or 							Skim milk- 27.9-42.7%	Skim milk- 0.003-0.006			

Table B.1. Fluindapyr and Major Metabolites/Degradate Structures.

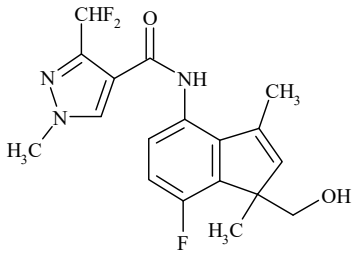
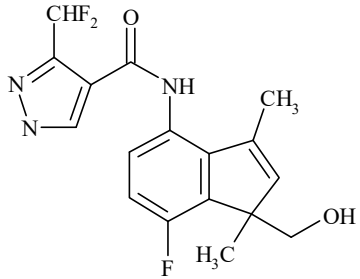
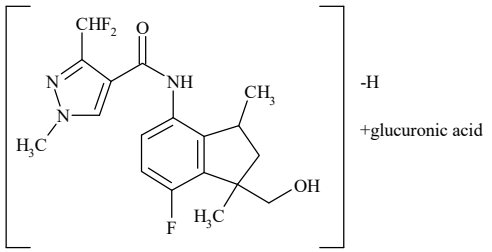
Name Structure	Major[1] Plant				Major Livestock NOR[3] Studies				Water		Rat
	Primary		Rotational		Poultry		Ruminant		Major [5]	Minor [6]	
	NOR[3]	MOR[4]	NOR[3]	MOR[4]	%TRR	ppm	%TRR	ppm			
1-OH-Me-deH-F9990 							Skim milk-14.5-14.9%	Skim milk-0.001-0.002			
1-OH-Me-DM-deH-F9990 							Skim milk-2.3-11.4%	Skim milk-<0.001-0.001			Bile-2.29% Urine-0.79% Feces-0.21%
1-OH-Me-F9990 glucuronide  -H +glucuronic acid							Liver-35.9-36.5% Kidney-42.1-57.2% Urine-55.4-58.9 Bile-49.9-51.7	Liver-0.100-0.079 Kidney-0.049-0.050 Urine-(NR[7]) Bile- (NR[7])			

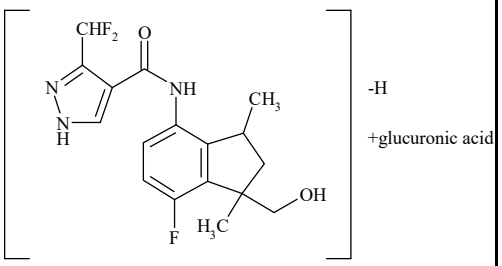
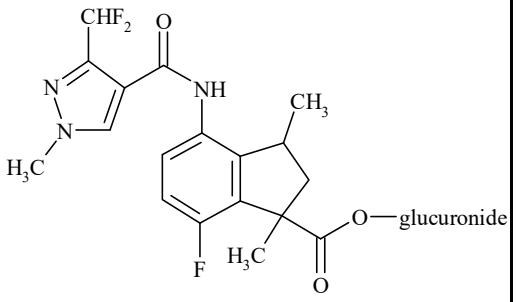
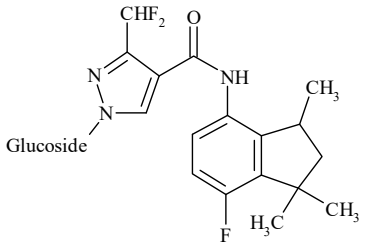
Table B.1. Fluindapyr and Major Metabolites/Degradate Structures.											
Name Structure	Major[1] Plant				Major Livestock NOR[3] Studies				Water		Rat
	Primary		Rotational		Poultry		Ruminant		Major [5]	Minor [6]	
	NOR[3]	MOR[4]	NOR[3]	MOR[4]	%TRR	ppm	%TRR	ppm			
1-OH-Me-DM-F9990 glucuronide  							Kidney-11.5-24.4% Urine-16.1-29.5% Bile-12.5-15.8%	Kidney-0.010-0.029 Urine-(NR[7]) Bile- (NR[7])			
1-COOH-F9990 glucuronide  							Bile-32.8-33.1%	Bile- (NR[7])			
DM-F9990-*N*-glucoside  	Soybean forage-11.13-15.15% Soybean hay-14.47-20.01%	Soybean forage-<0.007-0.321 ppm (0.120±0.089) Soybean hay-<0.007-1.31 ppm (0.315±0.224) Soybean seed-<0.007-0.012 ppm (0.007±0.001) Wheat whole plant (14-day PHI)-<0.010 ppm Wheat grain-<0.010 ppm Wheat straw-									

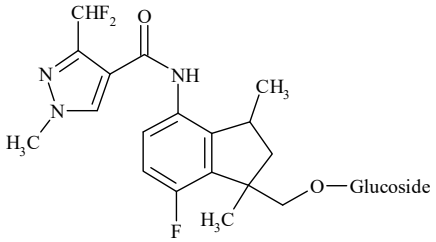
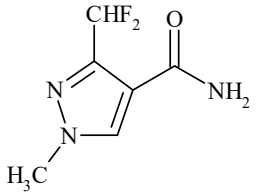
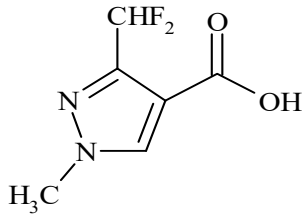
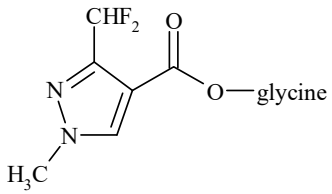
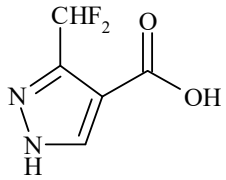
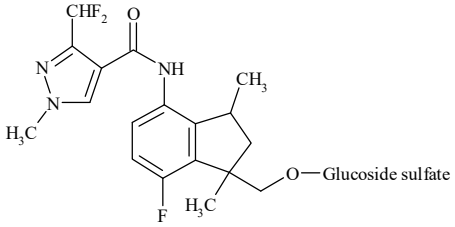
Table B.1. Fluindapyr and Major Metabolites/Degradate Structures.											
Name Structure	Major[1] Plant				Major Livestock NOR[3] Studies				Water		Rat
	Primary		Rotational		Poultry		Ruminant		Major [5]	Minor [6]	
	NOR[3]	MOR[4]	NOR[3]	MOR[4]	%TRR	ppm	%TRR	ppm			
		<0.010 ppm									
1-OH-Me-F9990-*O*-glucoside 	Soybean hay-6.11-19.43%										
Pyrazole carboxamide 	Soybean seed-35.65%									Soil photolysis- 4.23-7.32% Aqueous photolysis- <10% Aerobic aquatic-0.97-1.93% Hydrolysis- ND Field studies-2.7-3.7%	
Pyrazole carboxylic acid 										Aerobic aquatic-2.90-4.81% Aqueous photolysis- trace Hydrolysis- ND	

Table B.1. Fluindapyr and Major Metabolites/Degradate Structures.

Name Structure	Major[1] Plant				Major Livestock NOR[3] Studies				Water		Rat
	Primary		Rotational		Poultry		Ruminant		Major [5]	Minor [6]	
	NOR[3]	MOR[4]	NOR[3]	MOR[4]	%TRR	ppm	%TRR	ppm			
Pyrazole acid-related fragments   (examples)	Soybean seed-36.49%										
1-OH-Me-F9990 glucosyl-sulfate conjugates 	Sugar beet immature tops-52.79-62.19%										

[1] Considered major if more than 10% of the total radioactive residue in the nature of the residue (metabolism) studies, or more than 10% of the total residues in the magnitude of the residue (crop field trials, processing, livestock feeding) studies. [2] Considered minor if less than 10% of the total radioactive residue in the nature of the residue (metabolism) studies, or less than 10% of the total residues in the magnitude of the residue (crop field trials, processing, livestock feeding) studies. [3] NOR = Nature of the Residue (metabolism) studies and/or Confined Rotational Crop studies (OCSPP Test Guideline nos. 860.1300 or 860.1850; OECD Test Guideline nos.). [4] MOR = Magnitude of the Residue studies, including Crop Field Trials, Processing Studies, Livestock Feeding studies, and Field Rotational Crop studies (OCSPP Test Guideline Nos. 860.1500, 860.1520, and 860.1900; OECD Test Guideline Nos). [5] Considered major if >10% of the applied dose at any interval.
[6] Considered minor if <10% of the applied dose at any interval. [7] NR = "Not reported"

Appendix C. Review of Human Research

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include studies from PHED 1.1, the AHETF database, and the ORETF database, are (1) subject to ethics review pursuant to 40 CFR 26, (2) have received that review, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have included review by the Human Studies Review Board. Descriptions of data sources, as well as guidance on their use, can be found at the Agency website